8. EPIDEMIOLOGIC STUDIES OF THE CARCINOGENICITY OF EXPOSURE TO DIESEL EMISSIONS

8.1. INTRODUCTION

Emissions from diesel engine exhaust are made up of toxicants that include oxides of nitrogen and sulfur, carbon monoxide, and particulate matter consisting of a carbon core with many organic compounds, especially the polycyclic aromatic hydrocarbons adsorbed on the surface. Diesel engine exhaust contains about 100 times more particulate matter than gasoline engine exhaust.

In this chapter, various mortality and morbidity studies of the health effects of exposure to diesel engine emissions are reviewed. Although an attempt was made to cover all the relevant studies, a number of studies are not included for several reasons. First, the change from steam to diesel engines in locomotives began in 1935 and was about 95% complete by 1959 (Garshick et al., 1988). Diesel buses also were introduced about the same time. Therefore, exposure to diesel exhaust was less common, and the follow-up period for studies conducted prior to 1959 (Raffle, 1957; Kaplan, 1959) was not long enough to cover the long latency period of lung cancer. The usefulness of these studies in evaluating the carcinogenicity of diesel exhaust is greatly reduced; thus, they are not considered here.

Second, hypothesis-generating studies were excluded from this review because their findings need subsequent confirmation by definitive studies (Silverman et al., 1983; Schenker et al., 1984; Buiatti et al., 1985; Flodin et al., 1987; Siemiatycki et al., 1988; Swanson et al., 1993; Cordier et al., 1993; Notani et al., 1993).

Third, studies in which exposure to diesel exhaust was uncertain or was defined as motor exhaust (which includes both gasoline and diesel exhaust) were excluded because they would have contributed little to the evaluation of the carcinogenicity of diesel exhaust (Waxweiler et al., 1973; Ahlberg et al., 1981; Stern et al., 1981; Vineis and Magnani, 1985; Gustafsson et al., 1986; Silverman et al., 1986; Jensen et al., 1987; Garland et al., 1988; Risch et al., 1988; Guberan et al., 1992).

Fourth, a study by Coggon et al. (1984) was not included because the occupational information abstracted from death certificates had not been validated; this would have resulted in limited information.

Three types of studies of the health effects of exposure to diesel engine emissions are reviewed in this chapter: (1) cohort studies, (2) case-control studies of lung cancer, and (3) case-control studies of bladder cancer. In the cohort studies, the cohorts of heavy construction equipment operators, railroad and locomotive workers, and bus garage employees were studied retrospectively to determine increased mortality and morbidity resulting from exposures to

varying levels of diesel emissions in the workplace. A total of nine cohort mortality (one of the mortality studies also included a nested lung cancer case-control study), ten lung cancer case-control, and seven bladder cancer case-control studies are considered in this section.

8.2. COHORT STUDIES

8.2.1. Waller (1981): Trends in Lung Cancer in London in Relation to Exposure to Diesel Fumes

A retrospective mortality study of a cohort of London transport workers was conducted to determine if there was an excess of deaths from lung cancer that could be attributed to diesel exhaust exposure. Nearly 20,000 male employees aged 45 to 64 were followed for the 25-year period between 1950 and 1974, constituting a total of 420,700 man-years at risk. These were distributed among five job categories: drivers, garage engineers, conductors, motormen or guards, and engineers (works). Most employees lived in the greater London area. Lung cancer cases occurring in this cohort were ascertained only from death certificates of individuals who died while still employed, or if retired, following diagnosis. Expected death rates were calculated by applying greater London death rates to the population at risk within each job category. Data were calculated in 5-year periods and 5-year age ranges, finally combining the results to obtain the total expected deaths in the required age range for the calendar period. A total of 667 cases of lung cancer was reported, compared with 849 expected, to give a mortality ratio of 79%. In each of the five job categories, the observed numbers were below those expected. Engineers in garages had the highest mortality ratio (90%), but this did not differ significantly from the other job categories. Environmental sampling was done at one garage, on 1 day in 1979, for benzo[*a*]pyrene concentrations and was compared with corresponding values recorded in 1957. Concentrations of benzo[*a*]pyrene recorded in 1957 were at least 10 times greater than those measured in 1979.

This study has several methodologic limitations. The lung cancer deaths ascertained for the study occurred while the worker was employed (the worker either died of lung cancer or retired after lung cancer was diagnosed). Although man-years at risk were based on the entire cohort, no attempt was made to trace or evaluate the individuals who had resigned from the London transport company for any other reason. Hence, information on resignees who may have had significant exposure to diesel exhaust, and lung cancer deaths among them, was not available for analysis. This fact may have led to a dilution effect, resulting in underascertainment of observed lung cancer deaths and underestimation of mortality ratios. Eligibility criteria for inclusion in the cohort, such as starting date and length of service with the company, were not specified. Because an external comparison group was used to obtain expected number of deaths, the resulting mortality ratios were less than 1; this may be a reflection of the "healthy worker

effect." Investigators also did not categorize the five job categories by levels of diesel exhaust exposure, nor did they use an internal comparison group to derive risk estimates.

The age range considered for this study was limited (45 to 64 years of age) for the period between 1950 and 1964. It is not clear whether this age range was applied to calendar year 1950 or 1964 or at the mid-point of the 25-year follow-up period. No analyses were presented either by latency or by duration of employment (surrogate for exposure). The environmental survey based on benzo[*a*]pyrene concentrations suggests that the cohort in its earlier years was exposed to much higher concentrations of environmental contaminants than currently exist. It is not clear when the reduction in benzo[a]pyrene concentration occurred because there are no environmental readings available between 1957 and 1979. It is also important to note that the concentrations of benzo[*a*]pyrene inside the garage in 1957 were not very different from those outside the garage, thus indicating that exposure for garage workers was not much different from that of the general population. Last, no data were collected on smoking habits.

8.2.2. Howe et al. (1983): Cancer Mortality (1965 to 1977) in Relation to Diesel Fume and Coal Exposure in a Cohort of Retired Railroad Workers

This is a retrospective cohort study of the mortality experience of 43,826 male pensioners of the Canadian National Railroad (CNR) between 1965 and 1977. Members of this cohort consisted of male CNR pensioners who had retired before 1965 and who were known to be alive at the start of that year, as well as those who retired between 1965 and 1977. The records were obtained from a computer file that is regularly updated and used by the company for payment of pensions. To receive a pension, each pensioner must provide, on a yearly basis, evidence that he is alive. Specific cause of death among members of this cohort was ascertained by linking these records to the Canadian Mortality Data Base, which contains records of all deaths registered in Canada since 1950. Of the 17,838 deaths among members of the cohort between 1965 and 1977, 16,812 (94.4%) were successfully linked to a record in the mortality file. A random sample manual check on unlinked data revealed that failure to link was due mainly to some missing information on the death records.

Occupation at time of retirement was used by the Department of Industrial Relations to classify workers into three diesel fume and coal dust exposure categories: (1) nonexposed, (2) possibly exposed, and (3) probably exposed. Person-years of observation were calculated and classified by age at observation in 5-year age groups (35 to 39, 40 to 44, . . ., 80 to 84, and $\geq$85 years). The observed deaths were classified by age at death for different cancers, for all cancers combined, and for all causes of death combined. Standard mortality ratios (SMRs) were then calculated using rates of the Canadian population for the period between 1965 and 1977.

Both total mortality (SMR = 95, $p<0.001$) and all cancer deaths (SMR = 99, $p>0.05$) were close to that expected for the entire cohort. Analysis by exposure to diesel fume levels in the three categories (nonexposed, possibly exposed, and probably exposed) revealed an increased relative risk for lung cancer among workers with increasing exposure to diesel fumes. The relative risk for nonexposed workers was presumed to be 1.0; for those possibly exposed, the relative risk was elevated to 1.2, which was statistically significant ($p=0.013$); and, for those probably exposed, it was elevated to 1.35, which was statistically highly significant ($p=0.001$). The corresponding rates for exposure to varying levels of coal dust were very similar at 1.00, 1.21 ($p=0.012$), and 1.35 ($p=0.001$), respectively. The trend tests were highly significant for both exposures ($p<0.001$). Analysis performed after the exclusion of individuals who worked in the maintenance of steam engines, and hence were exposed to high levels of asbestos, yielded the risk of lung cancer to be 1.00, 1.21, and 1.33 for those nonexposed, possibly exposed, and probably exposed to diesel exhaust, respectively, with a highly significant trend ($p<0.001$).

An analysis done on individuals who retired prior to 1950 showed the relative risk of lung cancer among nonexposed, possibly exposed, and probably exposed to be 1.00, 0.70, and 0.44, respectively, based on fewer than 15 deaths in each category. A similar analysis of individuals who retired after 1950 found the results in the same categories to be 1.00, 1.23, and 1.40, respectively. Although retirement prior to 1950 indicated exposure to coal dust alone, retirement after 1950 shows the results of mixed exposure to coal dust and diesel fumes. As there was considerable overlap between occupations involving probable exposure to diesel fumes and probable exposure to coal dust, and as most members of the cohort were employed during the years in which the transition from coal to diesel occurred, it was difficult to distinguish whether lung cancer was associated with exposure to coal dust or diesel fumes or a mixture of both.

Although this study showed a highly significant dose-response relationship between diesel fumes and lung cancer, it has some methodological limitations. There were concurrent exposures to both diesel fumes and coal dust during the transition period; therefore, misclassification of exposure may have occurred, because only occupation at retirement was available for analysis. It is possible that the elevated response observed for lung cancer was due to the combined effects of exposure to both coal dust and diesel fumes and not just one or the other. However, it should be noted that so far coal dust has not been demonstrated to be a pulmonary carcinogen in studies of coal miners. No information was provided on duration of employment in either diesel work or the coal dust-related jobs for other than those jobs held at retirement. Therefore, it was not possible to evaluate whether this omission would have led to an under- or overestimate of the true relative risk. Furthermore, a lack of information on potential confounders such as smoking makes the interpretation of the excess risk of lung cancer even more difficult. Information on cause of death

was acquired from the mortality data linkage. There is a possibility that the cause of death may have been misclassified because of miscoding of the underlying cause of death.

8.2.3. Rushton et al. (1983): Epidemiological Survey of Maintenance Workers in the London Transport Executive Bus Garages and Chiswick Works

This is a retrospective mortality cohort study of male maintenance workers employed for at least 1 continuous year between January 1, 1967, and December 31, 1975, at 71 London transport bus garages (also known as rolling stock) and at Chiswick Works. For all men, the following information was obtained from computer listings: surname with initials, date of birth, date of joining company, last or present jobs, and location of work. For those individuals who left their job, date of and reason for leaving were also obtained. For those who died in service or after retirement and for men who had resigned, full name and last known address were obtained from an alphabetical card index in the personnel department. Additional tracing of individuals who had left was carried out through social security records. The area of their residence was assumed to be close to their work; therefore their place of work was coded as their residence. One hundred different job titles were coded into 20 broader groups. These 20 groups were not ranked for diesel exhaust exposure, though. The reason for leaving was coded as died in service, retired, or other. The underlying cause of death was coded using the eighth revision of the International Classification of Diseases (ICD). Person-years were calculated from date of birth and dates of entry to and exit from the study using the man-years computer language program. These were then subdivided into 5-year age and calendar period groups. The expected number of deaths was calculated by applying the 5-year age and calendar period death rates of the comparison population to the person-years of corresponding groups. The mortality experience of the male population in England and Wales was used as the comparison population. Significance values were calculated for the difference between the observed and expected deaths, assuming a Poisson distribution.

The number of person-years of observation totaled 50,008 and was contributed by 8,490 individuals in the study with a mean follow-up of 5.9 years. Only 2.2% (194) of the men were not traced. Observed deaths from all causes were significantly lower than expected (observed = 495, $p<0.001$). The observed deaths from all neoplasms and cancer of the lung were approximately the same as those expected. The only significant excess observed for cancer of the liver and gall bladder at Chiswick Works was based on four deaths ($p<0.05$). A few job groups showed a significant excess of risks for various cancers. All the excess deaths observed for the various job groups, except for the general hand category, were based on very small numbers (usually smaller than five) and merited cautious interpretation. Only a notable excess in the general hand category for lung cancer was based on 48 cases (SMR = 133, $p<0.03$). However, given the fact that there

was no adjustment for confounding variables such as smoking, the result should be interpreted cautiously.

This mortality study of London transport maintenance workers did not demonstrate any cancer excesses based on a large number of cases; this needs further exploration. Its limitations, including the small sample size, short duration of follow-up (average of only 6 years), and lack of sufficient latency period, make this study inadequate to draw any conclusions. The number of deaths by different causes and among the various job groups was too small to allow any meaningful conclusions. Details of work history were not obtained to permit any analysis by diesel exhaust exposure. Death information was ascertained from death certificates, with inherent problems of inaccuracy, misdiagnosis, and errors in coding, and it was not known whether a trained nosologist coded the death certificates. No adjustments were made for the confounding effects of smoking and socioeconomic factors.

8.2.4. Wong et al. (1985): Mortality Among Members of a Heavy Construction Equipment Operators Union With Potential Exposure to Diesel Exhaust Emissions

This is a retrospective mortality study conducted on a cohort of 34,156 male members of a heavy construction equipment operators union with potential exposure to diesel exhaust emissions. Study cohort members were identified from records maintained at Operating Engineers' Local Union No. 3-3A in San Francisco, CA. This union has maintained both work and death records on all its members since 1964. Individuals with at least 1 year of membership in this union between January 1, 1964, and December 31, 1978, were included in the study. Work histories of the cohort were obtained from job dispatch computer tapes. The study follow-up period was from January 1964 to December 1978. Death information was obtained from a trust fund, which provided information on retirement dates, vital status, and date of death for those who were entitled to retirement and death benefits. Approximately 50% of the cohort had been union members for less than 15 years, whereas the other 50% had been union members for 15 years or more. The average duration of membership was 15 years. As of December 31, 1978, 29,046 (85%) cohort members were alive, 3,345 (9.8%) were dead, and 1,765 (5.2%) remained untraced. Vital status of 10,505 members who had left the union as of December 31, 1978, was ascertained from the Social Security Administration. Death certificates were obtained from appropriate state health departments. Altogether, 3,243 deaths (for whom death certificates were available) in the cohort were coded using the seventh revision of the ICD. For 102 individuals, death certificates could not be obtained, only the date of death; these individuals were included in the calculation of the SMR for all causes of death but were deleted from the cause-specific SMR analyses. Expected deaths and SMRs were calculated using the U.S. national age-sex-race cause-

specific mortality rates for 5-year time periods between 1964 and 1978. The entire cohort population contributed to 372,525.6 person-years in this 5-year study period.

A total of 3,345 deaths was observed, compared with 4,109 expected. The corresponding SMR for all causes was 81.4 (p=0.01), which confirmed the "healthy worker effect." A total of 817 deaths was attributed to malignant neoplasms, slightly fewer than the 878.34 expected based on U.S. white male cancer mortality rates (SMR = 93.0, p=0.05). Mostly there were SMR deficits for cause-specific cancers, including lung cancer for the entire cohort (SMR = 98.6, observed = 309). The only significant excess SMR was observed for cancer of the liver (SMR = 166.7, observed = 23, p<0.05).

Analysis by length of union membership as a surrogate of duration for potential exposure showed statistically significant increases in SMRs of cancer of the liver (SMR = 424, p<0.01) in the 10- to 14-year membership group and of the stomach (SMR = 248, p<0.05) in the 5- to 9-year membership group. No cancer excesses were observed in the 15- to 19-year and 20+-year membership groups. Although the SMR for cancer of the lung had a statistically significant deficit in the less than 5-year duration group, it showed a positive trend with increasing length of membership, which leveled off after 10 to 14 years.

Cause-specific mortality analysis by latency period showed a positive trend for SMRs of all causes of death, although all of them were statistically significant deficits, reflecting the diminishing "healthy worker effect." This analysis also demonstrated a statistically significant SMR excess for cancer of the liver (10- to 19-year group, SMR = 257.9). The SMR for cancer of the lung showed a statistically significant deficit for a <10-year latency but showed a definite positive trend with increasing latency.

In addition to these analyses of the entire cohort, similar analyses were carried out in various subcohorts. Analyses of retirees, 6,678 individuals contributing to 32,670.1 person-years, showed statistically significant increases (p<0.01) in SMRs for all cancers; all causes of death; cancers of the digestive system, large intestine, respiratory system, and lung; emphysema; and cirrhosis of the liver. The other two significant excesses (p<0.01) were for lymphosarcoma and reticulosarcoma and nonmalignant respiratory diseases. Further analysis of the 4,075 retirees (18,677.8 person-years), who retired at age 65 or who retired earlier but had reached the age of 65 revealed statistically significant SMR increases (p<0.05) for all cancers, cancer of the lung, and lymphosarcoma and reticulosarcoma.

To analyze cause-specific mortality by job held (potential exposure to diesel exhaust emissions), 20 functional job titles were used, which were further grouped into three potential categories: (1) high exposure, (2) low exposure, and (3) unknown exposure. A person was classified in a job title if he ever worked on that job. Based on this classification system, if a person had ever worked in a high-exposure job title he was included in that group, even though he

may have worked for a longer time in a low-exposure group or in an unknown exposure group. Information on length of work in any particular job, hence indirect information on potential length of exposure, was not available either.

For the high-exposure group a statistically significant excess was observed for cancer of the lung among bulldozer operators who had 15 to 19 years of membership and 20+ years of follow-up (SMR = 343.4, $p<0.05$). This excess was based on 5 out of 495 deaths observed in this group of 6,712 individuals, who contributed 80,327.6 person-years of observation.

The cause-specific mortality analysis in the low-exposure group revealed statistically significant SMR excesses in individuals who had ever worked as engineers. These excesses were for cancer of the large intestine (SMR = 807.2, observed = 3, $p<0.05$) among those with 15 to 19 years of membership and length of follow-up of at least 20 years, and cancer of the liver (SMR = 871.9, observed = 3, $p<0.05$) among those with 10 to 14 years of membership and length of follow-up of 10 to 19 years. There were 7,032 individuals who contributed to 78,402.9 person-years of observation in the low-exposure group.

For the unknown exposure group, a statistically significant SMR was observed for motor vehicle accidents only (SMR = 173.3, observed = 21, $p<0.05$). There were 3,656 individuals who contributed to 33,388.1 person-years of observation in this category.

No work histories were available for those who started their jobs before 1967 and for those who held the same job prior to and after 1967. This constituted 9,707 individuals (28% of the cohort) contributing to 104,447.5 person-years. Statistically significant SMR excesses were observed for all cancers (SMR = 112, observed = 339, $p<0.05$) and cancer of the lung (SMR = 119.3, observed = 141, $p<0.01$). A significant SMR elevation was also observed for cancer of the stomach (SMR = 199.1, observed = 30, $p<0.01$).

This study demonstrates a statistically significant excess for cancer of the liver but also shows statistically significant deficits in cancers of the large intestine and rectum. It may be, as the authors suggested, that the liver cancer cases were actually cases resulting from metastases from the large intestine and/or rectum, since tumors of these sites will frequently metastasize to the liver. The excess in liver cancer mortality and the deficits in mortality that are due to cancer of the large intestine and rectum could also, as the authors indicate, be due to misclassification. Both possibilities have been considered by the investigators in their discussion.

Cancer of the lung showed a positive trend with length of membership as well as with latency, although none of the SMRs were statistically significant except for the workers without any work histories. The individuals without any work histories may have been the ones who were in their jobs for the longest period of time, because workers without job histories included those who had the same job before and after 1967 and thus may have worked 12 to 14 years or longer. If they had belonged to the category in which heavy exposure to diesel exhaust emissions was

very common for this prolonged time, then the increase in lung cancer, as well as stomach cancer, might be linked to diesel exhaust. Further information on those without work histories should be obtained if possible because such information may be quite informative with regard to the evaluation of the carcinogenicity of diesel exhaust.

The study design is adequate, covers about a 15-year observation period, has a large enough population, and is appropriately analyzed; however, it has too many limitations to permit any conclusions. First, no exposure histories are available. One has to make do with job histories, which provide limited information on exposure level. Any person who ever worked at the job or any person working at the same job over any period of time is included in the same category; this would have a dilution effect, since extremely variable exposures were considered in the study. Second, the length of time worked in any particular job is not available. Third, work histories were not available for 9,707 individuals, who contributed 104,447.5 person-years, a large proportion of the study cohort (28%). These individuals happen to show the most evidence of a carcinogenic effect. Confounding by alcohol consumption for cancer of the liver and smoking for emphysema and cancer of the lung was not ruled out. Last, although 34,156 members were eligible for the study, the vital status of 1,765 individuals was unknown. Nevertheless, they were still considered in the denominator of all the analyses. The investigators fail to mention how the person-year calculation for these individuals was handled. Also, some of the person-years might have been overestimated, as people may have paid the dues for a particular year and then left work. These two causes of overestimation of the denominator may have resulted in some or all the SMRs being underestimated.

As for the smoking survey, the investigators took a very small sample (133 out of 34,156, which was not even 1%). Of 133, only 107 (80%) participated. It was a systematic sample, but the authors neglected to mention how the list was prepared. Hence, the sample may not be representative of the study population and, with a small sample size, the results are not generalizable. The questionnaire asked only for current smoking history. No detailed history was obtained for the amount smoked or length of smoking history, both of which have a bearing on emphysema as well as lung carcinoma.

8.2.5. Edling et al. (1987): Mortality Among Personnel Exposed to Diesel Exhaust

This is a retrospective cohort mortality study of bus company employees, which investigated a possible increased mortality in cardiovascular diseases and cancers from diesel exhaust exposure. The cohort comprised all males employed at five different bus companies in southeastern Sweden between 1950 and 1959. Based on information from personnel registers, individuals were classified into one or more categories and could have contributed person-years at risk in more than one exposure category. The study period was from 1951 to 1983; information

was collected from the National Death Registry, and copies of death certificates were obtained from the National Bureau of Statistics. Workers who died after age 79 were excluded from the study because diagnostic procedures were likely to be more uncertain at higher ages (according to investigators). The cause-, sex-, and age-specific national death rates in Sweden were applied to the 5-year age categories of person-years of observation to determine expected deaths for all causes, malignant diseases, and cardiovascular diseases. A Poisson distribution was used to calculate p-values and confidence limits for the ratio of observed to expected deaths. The total cohort of 694 men (after loss of 5 men to follow-up) was divided into three exposure categories: (1) clerks with the lowest exposure, (2) bus drivers with moderate exposure, and (3) bus garage workers with highest exposure.

The 694 men provided 20,304 person-years of observation, with 195 deaths compared with 237 expected. A deficit in cancer deaths largely accounted for this lower-than-expected mortality in the total cohort. Among subcohorts, no difference between observed and expected deaths for total mortality, total cancers, or cardiovascular causes was observed for clerks (lowest diesel exposure), bus drivers (moderate diesel exposure), and garage workers (high diesel exposure). The risk ratios for all three categories were less than 1 except for cardiovascular diseases among bus drivers, which was 1.1.

When the analysis was restricted to members who had at least a 10-year latency period and either any exposure or an exposure exceeding 10 years, similar results were obtained, with fewer neoplasms than expected, whereas cardiovascular diseases showed risk around or slightly above unity.

Five lung cancer deaths were observed among bus drivers who had moderate diesel exhaust exposure, whereas 7.2 were expected. The only other lung cancer death was observed among bus garage workers who had the highest diesel exhaust exposure. The small size of the cohort and poor data on diesel exhaust exposure are among the major limitations of this study. Although lifetime occupational histories were available, no industrial hygiene data were presented to validate the classification of workers into low, moderate, and high exposure to diesel exhaust based on job title. The power of the present study was estimated to be 80% to detect a relative risk of 1.2 for cardiovascular diseases and 1.4 for cancers, but for specific cancer sites, the power was much lower than this. No information was available on confounding effects of smoking and asbestos exposure at the work sites.

8.2.6. Boffetta and Stellman (1988): Diesel Exhaust Exposure and Mortality Among Males in the American Cancer Society Prospective Study

Boffetta and Stellman conducted a mortality analysis of 46,981 males whose vital status was known at the end of the first 2 years of follow-up. The analysis was restricted to males aged

40 to 79 years in 1982 who enrolled in the American Cancer Society's prospective mortality study of cancer. Mortality was analyzed in relation to exposure to diesel exhaust and to employment in selected occupations related to diesel exhaust exposure. In 1982, more than 77,000 American Cancer Society volunteers enrolled over 1.2 million men and women from all 50 states, the District of Columbia, and Puerto Rico in a long-term cohort study, the Cancer Prevention Study II (CPS-II). Enrollees were usually friends, neighbors, or relatives of the volunteers; enrollment was by family groups with at least one person in the household 45 years of age or older. Subjects were asked to fill out a four-page confidential questionnaire and return it in a sealed envelope. The questionnaire included history of cancer and other diseases; use of medications and vitamins; menstrual and reproductive history; occupational history; and information on diet, drinking, smoking, and other habits. The questionnaire also included three questions on occupation: (1) current occupation, (2) last occupation, if retired, and (3) job held for the longest period of time, if different from the other two. Occupations were coded to an ad hoc two-digit classification in 70 categories. Exposures at work or in daily life to any of the 12 groups of substances were also ascertained. These included diesel engine exhausts, asbestos, chemicals/acids/solvents, dyes, formaldehyde, coal or stone dusts, and gasoline exhausts. Volunteers checked whether their enrollees were alive or dead and recorded the date and place of all deaths every other year during the study. Death certificates were then obtained from state health departments and coded according to a system based on the ninth revision of the ICD by a trained nosologist.

The data were analyzed to determine the mortality for all causes and lung cancer in relation to diesel exhaust exposure, mortality for all causes and lung cancer in relation to employment in selected occupations with high diesel exhaust exposure, and mortality from other causes in relation to diesel exhaust exposure. The incidence-density ratio was used as a measure of association, and test-based confidence limits were calculated by the Miettinen method. For stratified analysis, the Mantel-Haenszel method was used for testing linear trends. Data on 476,648 subjects comprising 939,817 person-years of risk were available for analysis. Three percent of the subjects (14,667) had not given any smoking history, and 20% (98,026) of them did not give information on diesel exhaust exposure and were therefore excluded from the main diesel exhaust analysis. Among individuals who had provided diesel exhaust exposure history, 62,800 were exposed and 307,143 were not exposed. Comparison of the population with known information on diesel exhaust exposure with the excluded population with no information on diesel exhaust exposure showed that the mean ages were 54.7 and 57.7 years, the nonsmokers were 72.4% and 73.2%, and the total mortality rates per 1,000 per year were 23.0% and 28.8%, respectively.

The all-cause mortality was elevated among railroad workers (relative risk [RR] = 1.43, 95% confidence interval [CI] = 1.2, 1.72), heavy equipment operators (RR = 1.7, 95% CI = 1.19,

2.44), miners (RR = 1.34, 95% CI = 1.06, 1.68), and truck drivers (RR = 1.19, 95% CI = 1.07, 1.31). For lung cancer mortality the risks were significantly elevated for miners (RR = 2.67, 95% CI = 1.63, 4.37) and heavy equipment operators (RR = 2.60, 95% CI = 1.12, 6.06). Risks were also elevated but not significantly for railroad workers (RR = 1.59, 95% CI = 0.94, 2.69) and truck drivers (RR = 1.24, 95% CI = 0.93, 1.66). These risks were calculated according to the Mantel-Haenszel method, controlling for age and smoking. Although the relative risk was nonsignificant for truck drivers, a small dose-response effect was observed when duration of diesel exhaust exposure for them was examined. For drivers who worked for 1 to 15 years, the relative risk was 0.87, while for drivers who worked for more than 16 years, the relative risk was 1.33 (95% CI = 0.64, 2.75). Relative risks for lung cancer were not presented for other occupations. Mortality analysis for other causes and diesel exhaust exposure showed a significant excess of deaths ($p<0.05$) in the following categories: cerebrovascular disease, arteriosclerosis, pneumonia, influenza, cirrhosis of the liver, and accidents.

The two main methodologic concerns in this study are the representativeness of the study population and the quality of information on exposure. The sample, though very large, was composed of volunteers. Thus, the cohort was healthier and less frequently exposed to important risk factors such as smoking and alcohol. Self-administered questionnaires were used to obtain data on occupation and diesel exhaust exposure. None of this information was validated. Nearly 20% of the individuals had an unknown exposure status to diesel exhaust, and they experienced a higher mortality for all causes and lung cancer than both the diesel exhaust exposed and unexposed groups. This could have introduced a substantial bias in the estimate of the association. Although only 0.8% of the subjects were lost to follow-up, the use of death certificates alone as a source of medical information poses problems in accuracy and coding. But the authors report that cancer deaths are routinely checked by histological confirmation from physicians or cancer registries. Given the fact that all diesel exhaust exposure occupations, such as heavy equipment operators, truck drivers, and railroad workers, showed elevated lung cancer risk, this study is suggestive of a causal association.

8.2.7. Garshick et al. (1988): A Retrospective Cohort Study of Lung Cancer and Diesel Exhaust Exposure in Railroad Workers

An earlier case-control study of lung cancer and diesel exhaust exposure in U.S. railroad workers by these investigators had demonstrated a relative odds of 1.41 (95% CI = 1.06, 1.88) for lung cancer with 20 years of work in jobs with diesel exhaust exposure. To confirm these results, a large retrospective cohort mortality study was conducted by the same investigators. Data sources for the study were the work records of the U.S. Railroad Retirement Board (RRB). The cohort was selected based on job titles in 1959, which was the year by which 95% of the

locomotives in the United States were diesel powered. Diesel exhaust exposure was considered to be a dichotomous variable depending on yearly job codes between 1959 and death or retirement through 1980. Industrial hygiene evaluations and descriptions of job activities were used to classify jobs as exposed or unexposed to diesel emissions. A questionnaire survey of 534 workers at one of the railroads where workers were asked to indicate the amount of time spent in railroad locations, either near or away from sources of diesel exhaust, was used to validate this classification. Workers selected for this survey were actively employed at the time of the survey, 40 to 64 years of age, who started work between 1939 and 1949, in the job codes sampled in 1959, and were eligible for railroad benefits. To qualify for benefits, a worker must have 10 years or more of service with the railroad and should not have worked for more than 2 years in a nonrailroad job after leaving railroad work. Workers with recognized asbestos exposure, such as repair of asbestos-insulated steam locomotive boilers, passenger cars, and steam pipes, or railroad building construction and repairs, were excluded from the job categories selected for study. However, a few jobs with some potential for asbestos exposure were included in the cohort, and the analysis was done both ways, with and without them.

The death certificates for all subjects identified in 1959 and reported by the RRB to have died through 1980 were searched. Twenty-five percent of them were obtained from the RRB and the remainder from the appropriate state departments of health. Coding of cause of death was done without knowledge of exposure history, according to the eighth revision of the ICD. If the underlying cause of death was not lung cancer, but was mentioned on the death certificate, it was assigned as a secondary cause of death, so that the ascertainment of all cases was complete. Workers not reported by the RRB to have died by December 31, 1980, were considered to be alive. Deceased workers for whom death certificates had not been obtained or, if obtained, did not indicate cause of death, were assumed to have died of unknown causes.

Proportional hazard models were fitted that provided estimates of relative risk for death caused by lung cancer using the partial likelihood method described by Cox, and 95% confidence intervals were constructed using the asymptotic normality of the estimated regression coefficients of the proportional hazards model. Exposure was analyzed by diesel exhaust-exposed jobs in 1959 and by cumulative number of years of diesel exhaust exposure through 1980. Directly standardized rate ratios for deaths from lung cancer were calculated for diesel exhaust exposed compared with unexposed for each 5-year age group in 1959. The standardized rates were based on the overall 5-year person-year time distribution of individuals in each age group starting in 1959. The only exception to this was between 1979 and 1980, when a 2-year person-year distribution was used. The Mantel-Haenszel analogue for person-year data was used to calculate 95% confidence intervals for the standardized rate ratios.

The cohort consisted of 55,407 workers, 19,396 of whom had died by the end of 1980. Death certificates were not available for 11.7% of all deaths. Of the 17,120 deaths for whom death certificates were obtained, 48.4% were attributable to diseases of the circulatory system, whereas 21% were attributable to all neoplasms. Of all neoplasms, 8.7% (1,694 deaths) were due to lung cancer. A higher proportion of workers in the younger age groups, mainly brakemen and conductors, were exposed to diesel exhaust, while a higher proportion of workers in the older age groups were potentially exposed to asbestos. In a proportional hazards model, analyses by age in 1959 found a relative risk of 1.45 (95% CI = 1.11, 1.89) among the age group 40 to 44 years and a relative risk of 1.33 (95% CI = 1.03, 1.73) for the age group 45 to 49 years. Risk estimates in the older age groups 50 to 54, 55 to 59, and 60 to 64 years were 1.2, 1.18, and 0.99, respectively, and were not statistically significant. The two youngest age groups in 1959 had workers with the highest prevalence and longest duration of diesel exhaust exposure and lowest exposure to asbestos. When potential asbestos exposure was considered as a confounding variable in a proportional hazards model, the estimates of relative risk for asbestos exposure were all near null value and not significant. Analysis of workers exposed to diesel exhaust in 1959 (n = 42,535), excluding the workers with potential past exposure to asbestos, yielded relative risks of 1.57 (95% CI = 1.19, 2.06) and 1.34 (95% CI = 1.02, 1.76) in the 1959 age groups 40 to 44 years and 45 to 49 years. Directly standardized rate ratios were also calculated for each 1959 age group based on diesel exhaust exposure in 1959. The results obtained confirmed those obtained by using the proportional hazards model.

Relative risk estimates were then obtained using duration of diesel exhaust exposure as a surrogate for dose. In a model that used years of exposure up to and including exposure in the year of death, no exposure duration-response relationship was obtained. When analysis was done by disregarding exposure in the year of death and 4 years prior to death, the risk of dying from lung cancer increased with the number of years worked in a diesel-exhaust-exposed job. In this analysis, exposure to diesel exhaust was analyzed by exposure duration groups and in a model entering age in 1959 as a continuous variable. The workers with greater than 15 years of exposure had a relative risk of lung cancer of 1.72 (95% CI = 1.27, 2.33). The risk for 1 to 4 years of cumulative exposure was 1.20 (95% CI = 1.01, 1.44); for 5 to 9 years of cumulative exposure, it was 1.24 (95% CI = 1.06, 1.44); and for 10 to 14 years of cumulative exposure, it was 1.32 (95% CI = 1.13, 1.56). Directly standardized rate ratios were also calculated for each 1959 age group based on diesel exposure in 1959. The results obtained confirmed those obtained by using the proportional hazards model.

The results of this study, demonstrating a positive association between diesel exhaust exposure and increased lung cancer, are consistent with the results of the case-control study conducted by the same investigators in railroad workers dying of lung cancer from March 1981

through February 1982. This cohort study has addressed many of the weaknesses of the other epidemiologic studies. The large sample size (60,000) allowed sufficient power to detect small risks and also permitted the exclusion of workers with potential past exposure to asbestos. The stability of job career paths in the cohort ensured that of the workers 40 to 44 years of age in 1959 classified as diesel exhaust-exposed, 94% of the cases were still in diesel exhaust-exposed jobs 20 years later.

The main limitation of the study is the lack of quantitative data on exposure to diesel exhaust. This is one of the few studies in which industrial hygiene measurements of diesel exhaust were done. These measurements were correlated with job titles to divide the cohort in dichotomous exposure groups of exposed and nonexposed. This may have led to an underestimation of the risk of lung cancer since exposed groups included individuals with low to high exposure. The number of years exposed to diesel exhaust was used as a surrogate for dose. The dose, based on duration of employment, may have been inaccurate because individuals were working on steam or diesel locomotives during the transition period. If the categories of exposure to diesel exhaust would have been set up as no, low, moderate, and high exposure, the results would have been more meaningful and so would have been the dose-response relationship. Another limitation of this study was the inability to examine the effect of years of exposure and latency. No adjustment for smoking was made in this study. However, an earlier case-control study done in the same cohort (Garshick et al., 1987) showed no significant difference in the risk estimate after adjusting for smoking. Despite these limitations, the results of this study demonstrate that occupational exposure to diesel exhaust is associated with a modest risk (1.5) of lung cancer.

8.2.8. Gustavsson et al. (1990): Lung Cancer and Exposure to Diesel Exhaust Among Bus Garage Workers

A retrospective mortality study (from 1952 to 1986), cancer incidence study (from 1958 to 1984), and nested case-control study were conducted among a cohort of 708 male workers from five bus garages in Stockholm, Sweden, who had worked for at least 6 months between 1945 and 1970. Thirteen individuals were lost to follow-up, reducing the cohort to 695.

Information was available on location of workplace, job type, and beginning and ending of work periods. Workers were traced using a computerized register of the living population, death and burial books, and data from the Stockholm city archives.

For the cohort mortality analyses, death rates of the general population of greater Stockholm were used. Death rates of occupationally active individuals, a subset of the general population of greater Stockholm, were used as a second comparison group to reduce the bias from “healthy worker effect.” Mortality analysis was conducted using the “occupational mortality

analysis program" (OCMAP-PC). For cancer incidence analysis, the "epidemiology in Linköping" (EPILIN) program was used, with the incidence rates obtained from the cancer registry.

For the nested case-control study, both dead and incident primary lung cancers, identified in the register of cause of deaths and the cancer register, were selected as cases (20). Six controls matched on age ±2 years, selected from the noncases at the time of the diagnosis of cases, were drawn at random without replacements. Matched analyses were done to calculate odds ratios using conditional logistic regression. The EGRET and Epilog programs were used for these analyses.

Diesel exhaust and asbestos exposure assessments were performed by industrial hygienists based on the intensity of exposure to diesel exhaust and asbestos, specific for workplace, work task, and calendar time period. A diesel exhaust exposure assessment was based on (1) amount of emission (number of buses, engine size, running time, and type of fuel), (2) ventilatory equipment and air volume of the garages, and (3) job types and work practices. Based on detailed historical data and very few actual measurements, relative exposures were estimated (these were not absolute exposure levels). The scale was set to 0 for unexposed and 1 for lowest exposure, with each additional unit increase corresponding to a 50% increase in successive intensity (i.e., 1.5, 2.25, 3.38, and 5.06).

Based on personal sampling of asbestos during 1987, exposures were estimated and time-weighted annual mean exposures were classified on a scale of three degrees (0, 1, and 2). Cumulative exposures for both diesel exhaust and asbestos were calculated by multiplying the level of exposure by the duration of every work period. An exposure index was calculated by adding for every individual contributions from all work periods for both diesel exhaust and asbestos. Four diesel exhaust index classes were created: 0 to 10, 10 to 20, 20 to 30, and >30. The four asbestos index classes were 0 to 20, 20 to 40, 40 to 60, and >60. The cumulative exposure indices were used for the nested case-control study.

Excesses were observed for all cancers and some other site-specific cancers using both comparison populations for the cohort mortality study, but none of them was statistically significant. Based on 17 cases, standardized mortality ratios (SMRs) for lung cancer were 122 and 115 using Stockholm occupationally active and general population, respectively. No dose-response was observed with increasing cumulative exposure. The cancer incidence study reportedly confirmed the mortality results (results not given).

The nested case-control study showed increasing risk of lung cancer with increasing exposure. Weighted linear regression gave RRs of 1.34 (95% CI = 1.09 to 1.64), 1.81 (95% CI = 1.20 to 2.71), and 2.43 (95% CI = 1.32 to 4.47) for the diesel exhaust indices 10 to 20, 20 to 30, and >30, respectively, using 0 to 10 as the comparison group. The study was based on 17 cases and six controls for each case matched on age ± 2 years. The results from conditional logistic

regression were similar to those obtained by weighted linear regression, but none was statistically significant. Adjustment for asbestos exposure did not change the lung cancer risk for diesel exhaust.

The main strength of this study is the detailed exposure matrices constructed for both diesel exhaust and asbestos exposure, although they were based primarily on job tasks and very few actual measurements. There are a few methodological limitations to this study. The cohort is small and there were only 17 lung cancer deaths, thus the power is low. Exposure or outcome may be misclassified, although any resulting bias in the relative risk estimates is likely to be toward unity, because exposure classification was done independently of the outcome. Although the analysis by dose indices was done, no latency analysis was performed. Finally, data on smoking were missing, thus potentially confounding the lung cancer results. The authors suggest that even the heaviest smoking among individuals who were heavily exposed to diesel exhaust will be unable to explain the excess relative risk of 2.4 observed in this group. This may be an overstatement, however, as cigarette smoking is a very strong risk factor for lung cancer. Overall, this study provides some support to the excess lung cancer results found earlier among populations exposed to diesel exhaust.

8.2.9. Hansen (1993): A Follow-Up Study on the Mortality of Truck Drivers

This is a retrospective cohort mortality study of unskilled male laborers, ages 15 to 74 years, in Denmark, identified from a nationwide census file of November 9, 1970. The exposed group included all truck drivers employed in the road delivery or long-haul business (14,225). The unexposed group included all laborers in certain selected occupational groups considered to be unexposed to fossil fuel combustion products and to resemble truck drivers in terms of work-related physical demands and various personal background characteristics (43,024).

Through automatic record linkage between the 1970 census register (the Central Population Register 1970 to 1980) and the Death Certificate Register (1970 to 1980), the population was followed for cause-specific mortality or emigration up to November 9, 1980. Expected number of deaths among truck drivers was calculated by using the 5-year age group and 5-year time period death rates of the unexposed group and applying them to the person-years accumulated by truck drivers. International Classification of Diseases Revision 8 was used to code the underlying cause of death. Test-based confidence intervals (CI) were calculated using Miettinen's method. A Poisson distribution was assumed for the smaller numbers, and CI was calculated based on exact Poisson distribution (Ciba-Geigy). Total person-years accrued by truck drivers were 138,302, whereas for the unexposed population, they were 407,780. There were 627 deaths among truck drivers and 3,811 deaths in the unexposed group. Statistically significant (SS) excesses were observed for all cancer mortality (SMR = 121, 95% CI = 104 to 140); cancer

of respiratory organs (SMR = 160, 95% CI = 128 to 198), which mainly was due to cancer of bronchus and lung (SMR = 160, 95% CI = 126 to 200); and multiple myeloma (SMR = 439, 95% CI = 142 to 1,024). When lung cancer mortality was further explored by age groups, excesses were observed in most of the age groups (30 to 39, 45 to 49, 50 to 54, 55 to 59, 60 to 64, and 65 to 74), but there were small numbers of deaths in each group when stratified by age, and the excesses were statistically significant for the 55 to 59 (SMR = 229, 95% CI = 138 to 358) and 60 to 64 (SMR = 227, 95% CI = 142 to 344) age groups only.

As acknowledged by the author, the study has quite a few methodologic limitations. The exposure to diesel exhaust is assumed in truck drivers based on diesel-powered trucks, but no validation of qualitative or quantitative exposure is attempted. It is also not known whether any of these truck drivers or any other laborers had changed jobs after the census of November 9, 1970, thus creating potential misclassification bias in exposure to diesel exhaust. The lack of smoking data and a 36% rural population (usually consuming less tobacco) in the unexposed group further confound the lung cancer results. The follow-up period is relatively short, and a latency analysis was not attempted. At best, the findings of this study are consistent with the findings of other truck driver studies.

Table 8-1 summarizes the foregoing cohort studies.

Table 8-1. Epidemiologic studies of the health effects of exposure to diesel exhaust: cohort mortality studies

Authors	Population studied	Diesel exhaust exposure assessment	Results	Limitations
Waller (1981)	Approximately 20,000 male London transportation workers Aged 45 to 64 years 25 years follow-up (1950-1974)	Five job categories used to define exposure Environmental benzo[a]pyrene concentrations measured in 1957 and 1979	SMR = 79 for lung cancer for the total cohort SMRs for all five job categories were less than 100 for lung cancer	Exposure measurement of benzo[a]pyrene showed very little difference between inside and outside the garage Incomplete information on cohort members No adjustment for confounding such as other exposures, cigarette smoking, etc. No latency analysis
Howe et al. (1983)	43,826 male pensioners of the Canadian National Railway Company Mortality between 1965 and 1977 among these pensioners was compared with mortality of general Canadian population.	Exposure groups classified by a group of experts based on occupation at the time of retirement Three exposure groups: Nonexposed Possibly exposed Probably exposed	RR = 1.2 (p=0.013) and RR = 1.3 (p=0.001) for lung cancer for possible and probable exposure, respectively A highly significant dose-response relationship demonstrated by trend test (p<0.001)	Incomplete exposure assessment due to lack of lifetime occupational history Mixed exposures to coal dust and diesel exhaust No validation of method was used to categorize exposure No data on smoking No latency analysis
Rushton et al. (1983)	8,490 male London transport maintenance workers Mortality of workers employed for 1 continuous year between January 1, 1967, and December 31, 1975, was compared with mortality of general population of England and Wales	100 different job titles were grouped in 20 broad categories The categories were not ranked for diesel exhaust exposure	SMR = 133 (p<0.03) for lung cancer in the general hand job group Several other job categories showed SS increased SMRs for several other sites based on fewer than five cases	Ill-defined diesel exhaust exposure without any ranking Average 6-year follow-up (i.e., not enough time for lung cancer latency) No adjustment for confounders such as smoking

Table 8-1. Epidemiological studies of the health effects of exposure to diesel exhaust: cohort mortality studies (continued)

Authors	Population studied	Diesel exhaust exposure assessment	Results	Limitations
Wong et al. (1985)	34,156 male heavy construction equipment operators Members of the local union for at least 1 year between January 1, 1964, and December 1, 1978	20 functional job titles grouped into three job categories for potential exposure Exposure groups (high, low, and unknown) based on job description and proximity to source of diesel exhaust emissions	SMR = 166 (p<0.05) for liver cancer for total cohort SMR = 343 (observed = 5, p<0.05) for lung cancer for high-exposure bulldozer operators with 15-19 years of membership, 20+ years of follow-up SMR = 119 (observed = 141, p<0.01) for workers with no work histories	No validation of exposure categories, which were based on surrogate information Incomplete employment records Employment history other than from the union not available No data on confounders such as other exposures, smoking, etc.
Edling et al. (1987)	694 male bus garage employees Follow-up from 1951 through 1983 Mortality of these men was compared with mortality of general population of Sweden	Three exposure groups based on job titles: High exposure, bus garage workers Intermediate exposure, bus drivers Low exposure, clerks	No SS differences were observed between observed and expected for any cancers by different exposure groups	Small sample size No validation of exposure No data on confounders such as other exposures, smoking, etc.
Boffetta and Stellman (1988)	46,981 male volunteers enrolled in the American Cancer Society's Prospective Mortality Study of Cancer in 1982 Aged 40 to 79 years at enrollment First 2-year follow-up	Self-reported occupations were coded into 70 job categories Employment in high diesel exhaust exposure jobs were compared with nonexposed jobs	Total mortality (SS) elevated for railroad workers, heavy equipment operators, miners, and truck drivers Lung cancer mortality (SS) elevated for miners and heavy equipment operators Lung cancer mortality (SNS) elevated among railroad workers and truck drivers Truck drivers also showed a small dose response	Exposure information based on self-reported occupation for which no validation was done Volunteer population, probably healthy population

Table 8-1. Epidemiological studies of the health effects of exposure to diesel exhaust: cohort mortality studies (continued)

Authors	Population studied	Diesel exhaust exposure assessment	Results	Limitations
Garshick et al. (1988)	55,407 white male railroad workers Aged 40 to 64 years in 1959 Started work 10-20 years earlier than 1959	Industrial hygiene data correlated with job titles to dichotomize the jobs as "exposed" or "not exposed"	RR = 1.45 (40-44 year age group) RR = 1.33 (45-49 year age group) Both SS After exclusion of workers exposed to asbestos RR = 1.57 (40-44 year age group) RR = 1.34 (45-49 year age group) Both SS Dose response indicated by increasing lung cancer risk with increasing cumulative exposure	Years of exposure used as surrogate for dose Not possible to separate the effect of time since first exposure and duration of exposure
Gustavsson et al. (1990)	695 male workers from 5 bus garages in Stockholm, Sweden, who had worked for 6 months between 1945 and 1970 34 years follow-up (1952-1986) Nested case-control study 17 cases, six controls for each case matched on age ± 2 years	Four diesel exhaust indices were created: 0 to 10, 10 to 20, 20-30, and >30 based on job tasks and duration of work	SMRs of 122 and 115 (OA and GP), respectively, SNS Case-control study results RR = 1.34 (10 to 20) RR = 1.81 (20 to 30) RR = 2.43 (>30) All SS with 0-10 as comparison group	Exposure matrix based on job tasks (not on actual measurements) Small cohort, hence low power Lack of smoking data
Hansen (1993)	Cohort of 57,249 unskilled laborers, ages 15 to 74, in Denmark (nationwide census file) November 9, 1970 Follow-up through November 9, 1980	Diesel exhaust exposure assumed based on diesel-powered trucks	SS SMR = 160 for bronchus and lung for total population	No actual exposure data available Lack of smoking data Job changes may have occurred from laborer to driver Short follow-up period

Abbreviations: RR = relative risk; SMR = standardized mortality ratio; SNS = statistically nonsignificant; SS = statistically significant; OA = occupationally active; GP = general population.

8.3. CASE-CONTROL STUDIES OF LUNG CANCER

8.3.1. Williams et al. (1977): Associations of Cancer Site and Type With Occupation and Industry From the Third National Cancer Survey Interview

This paper reports findings of the analysis of the Third National Cancer Survey (TNCS). The lifetime histories, occupations, and industries were studied for associations with specific cancer sites and types after controlling for age, sex, race, education, use of cigarettes or alcohol, and geographic location. Of 13,179 cancer patients, a 10% random sample of all incident invasive cancers in eight areas, a total of 7,518 were successfully interviewed in the 3 years surveyed by the TNCS. These comprised 57% of those eligible to participate. The interview included items on use of tobacco and alcohol (by type, amount, and duration), family income, patient education, and employment history. Actual descriptions of the occupation and industry were recorded by interviewers and were coded separately for main lifetime employment, recent employment, and other jobs held according to the 1970 Census Coding Scheme. Occupations or industries were combined to form larger groups. Coding of occupational and industrial labels in meaningful job categories was done by one of the authors. Of the 3,539 interviewed males and 3,937 interviewed females, 95% and 84%, respectively, listed some main employment. The basic analysis consisted of an intercancer comparison and involved comparing the proportions of specific main lifetime industries and occupations among patients with cancer at one site with those of patients having cancer at other sites combined as a control group; this was done using a series of Mantel-Haenszel stratified contingency table analyses to yield odds ratios and chi-square values. Odds ratios (ORs) were computed separately for males and females, controlling for age, race, education, tobacco, alcohol, and geographic location.

A total of 432 and 128 lung cancers were present in males and females, respectively. For males, an excess risk of lung cancer was observed for the following main industrial groups: mines (OR = 1.21), construction (OR = 1.24), transportation (OR = 1.17), utility and sanitary services (OR = 2.79, $p<0.05$), and professional (OR = 1.41). An excess of bladder cancer was reported for the mining industry (OR = 1.61). For females, an excess of lung cancer was detected for the transportation industry (OR = 1.96); finance and retail industry (OR = 1.73); and the business, car repair, and miscellaneous service industry (OR = 2.29). None of these excesses were statistically significant. All of these odds ratios were adjusted for age, race, education, tobacco, alcohol, and geographic location. The transportation industry for males and females also showed a nonsignificant excess risk for cancers of the liver and gall bladder ducts. When the analysis was done for specific lifetime industries, the odds ratio for lung cancer in males was 1.40 for railroad workers and 1.34 for truck drivers. Both of these excesses were statistically nonsignificant.

The strengths of the TNCS interview data set are its large size, histological confirmation of nearly 95% of diagnoses, availability of information on occupation, and details of confounding

variables obtained by personal interview and ability to control for them. Among its weaknesses are a 47% nonresponse rate and the fact that the population surveyed came from predominantly urban areas and did not represent many industries. Also, most of the associations observed did not achieve statistical significance because they were based on small numbers of patients who had both specific cancers and specific types of employment. The control group was the combined "other cancers," which may have diluted the association because diesel exhaust is also suspected of being associated with bladder cancer, and this category was included in the control group when the comparison was made with lung cancer. The study presented several tables, but the total population in each table was different and never added up to the initial number interviewed. The authors failed to explain these omissions. Further, when multiple comparisons are made, some significant associations arise by chance. This analysis suggests an association with lung cancer for three industries with potential diesel exhaust exposure: trucking, railroading, and mining.

8.3.2. Hall and Wynder (1984): A Case-Control Study of Diesel Exhaust Exposure and Lung Cancer

Hall and Wynder conducted a case-control study of 502 male lung cancer cases and 502 controls without tobacco-related diseases that examined an association between occupational diesel exhaust exposure and lung cancer. Histologically confirmed primary lung cancer patients who were 20 to 80 years old were ascertained from 18 participating hospitals in six U.S. cities, 12 months prior to the interview. Eligible controls, patients at the same hospitals without tobacco-related diseases, were matched to cases by age (±5 years), race, hospital, and hospital room status. The number of male lung cancer cases interviewed totaled 502, which was 64% of those who met the study criteria for eligibility. Of the remaining 36%, 8% refused, 21% were too ill or had died, and 7% were unreliable. Seventy-five percent of eligible controls completed interviews. Of these interviewed controls, 49.9% were from the all-cancers category, whereas 50.1% were from the all-noncancers category. All interviews were obtained in hospitals to gather detailed information on smoking history, coffee consumption, artificial sweetener use, residential history, and abbreviated medical history as well as standard demographic variables. Occupational information was elicited by a question on the usual lifetime occupation and was coded by the abbreviated list of the U.S. Bureau of Census Codes. The odds ratios were calculated to evaluate the association between diesel exhaust exposure and risk of lung cancer incidence. Summary odds ratios were computed by the Mantel-Haenszel method after adjusting for potential confounding by age, smoking, and socioeconomic class. Two-sided, 95% confidence intervals were computed by Woolf's method. Occupational exposure to diesel exhaust was defined by two criteria. First, occupational titles were coded "probably high exposure" as defined by the industrial hygiene standards established for the various jobs. The job titles included under this

category were warehousemen, bus and truck drivers, railroad workers, and heavy equipment operators and repairmen. The second method used the National Institute for Occupational Safety and Health (NIOSH) criteria to analyze occupations by diesel exposure. In this method, the estimated proportion of exposed workers was computed for each occupational category by using the NIOSH estimates of the exposed population as the numerator and the estimates of individuals employed in each occupational category from the 1970 census as the denominator. Occupations estimated to have at least 20% of their employees exposed to diesel exhaust were defined as "high exposure," those with 10 to 19% of their employees exposed were defined as "moderate exposure," and those with less than 10% of their employees exposed were defined as "low exposure."

Cases and controls were compared with respect to exposure. The relative risk was 2.0 (95% CI = 1.2, 3.2) for those workers who were exposed to diesel exhaust versus those who were not. The risk, however, decreased to a nonsignificant 1.4 when the data were adjusted for smoking. Analysis by NIOSH criteria found a nonsignificant relative risk of 1.7 in the high-exposure group. There were no significantly increased cancer risks by occupation either by the first method or by the NIOSH method. To assess any possible synergism between diesel exhaust exposure and smoking, the lung cancer risks were calculated for different smoking categories. The relative risks were 1.46 among nonsmokers and ex-smokers, 0.82 among current smokers of $\leq$20 cigarettes/day, and 1.3 among current smokers of 20+ cigarettes/day, indicating a lack of synergistic effects.

The major strength of this study is the availability of a detailed smoking history for all the study subjects. However, this is offset by the lack of diesel exhaust exposure measurements, use of a poor surrogate for exposure, and lack of consideration of latency period. Information was collected on only one major lifetime occupation, and it is likely that those workers who had more than one major job may not have reported the occupation with the heaviest diesel exhaust exposures. Further, occupational histories were obtained from self-reports and were not validated with work records. This could have resulted in recall bias and misclassification of exposure status.

8.3.3. Damber and Larsson (1987): Occupation and Male Lung Cancer, a Case-Control Study in Northern Sweden

A case-control study of lung cancer was conducted in northern Sweden to determine the occupational risk factors that could explain the large geographic variations of lung cancer incidence in that country. The study region comprised the three northernmost counties of Sweden, with a total male population of about 390,000. The rural municipalities with 15% to 20% of the total population have forestry and agriculture as dominating industries, and the urban

areas have a variety of industrial activities (mines, smelters, steel factories, paper mills, and mechanical workshops). All male cases of lung cancer reported to the Swedish Cancer Registry during the 6-year period between 1972 and 1977, who had died before the start of the study, were selected. Of 604 eligible cases, 5 did not have microscopic confirmation and in another 5 the diagnosis was doubtful, but these cases were included nevertheless. Cases were classified as small carcinomas, squamous cell carcinomas, adenocarcinomas, and other types. For each case a dead control was drawn from the National Death Registry matched by sex, year of death, age, and municipality. Deaths in controls classified as lung cancer and suicides were excluded. A living control matched to the case by sex, year of birth, and municipality was also drawn from the National Population Registry. Postal questionnaires were sent to close relatives of cases and dead controls, and to living controls themselves to collect data on occupation, employment, and smoking habits. Replies were received from 589 cases (98%), 582 surrogates of dead controls (96%), and 453 living controls (97%).

Occupational data were collected on occupations or employment held for at least 1 year and included type of industry, company name, task, and duration of employment. Supplementary telephone interviews were performed if occupational data were lacking for any period between age 20 and time of diagnosis. Data analysis involved calculation of the odds ratios by the exact method based on the hypergeometric distribution and the use of a linear logistic regression model to adjust for the potential confounding effects of smoking. Separate analyses were performed with dead and living controls, and on the whole there was good agreement between the two control groups. A person who had been active for at least 1 year in a specific occupation was in the analysis assigned to that occupation.

Using dead controls, the odds ratios adjusted for smoking were 1.0 (95% CI = 0.7, 1.5) and 2.7 (95% CI = 1.0, 8.1) for professional drivers ($\geq$1 year of employment) and underground miners ($\geq$1 year of employment), respectively. For 20 or more years of employment in those occupations, the odds ratios adjusted for smoking were 1.2 (95% CI = 0.6, 2.2) and 9.8 (95% CI = 1.5, 414). These were the only two occupations listed with potential diesel exhaust exposure. An excess significant risk was detected for copper smelter workers, plumbers, and electricians, as well as concrete and asphalt workers. Occupational asbestos exposure was also associated with an elevated odds ratio of 2.6 (95% CI = 1.6, 3.6) for $\geq$1 year of employment and 3.6 (95% CI = 1.9, 7.2) for $\geq$20 years of employment. All the odds ratios were calculated by adjusting for age, smoking, and municipality. After comparison with the live controls, the odds ratios were found to be lower than those observed with dead controls. None of the odds ratios were statistically significant in this comparison.

This study did not detect any excess risk of lung cancer for professional drivers, who, among all the occupations listed, had the most potential for exposure to motor vehicle exhaust.

However, it is not known whether these drivers were exposed exclusively to gasoline exhaust, diesel exhaust, or varying degrees of both. An excess risk was detected for underground miners, but it is not known if this was due to diesel emissions from engines or from radon daughters in poorly ventilated mines. Although a high response rate (98%) was obtained by the postal questionnaires, the use of surrogate respondents is known to lead to misclassification errors that can bias the odds ratio to 1.

8.3.4. Lerchen et al. (1987): Lung Cancer and Occupation in New Mexico

This is a population-based case-control study conducted in New Mexico that examines the association between occupation and occurrence of lung cancer in Hispanic and non-Hispanic whites. Cases involved residents of New Mexico, 25 through 84 years of age and diagnosed between January 1, 1980, and December 31, 1982, with primary lung cancer, excluding bronchioalveolar carcinoma. Cases were ascertained through the New Mexico Tumor Registry, which is a member of the Surveillance Epidemiology and End Results (SEER) Program of the National Cancer Institute. Controls were chosen by randomly selecting residential telephone numbers and, for those over 65 years of age, from the Health Care Financing Administration's roster of Medicare participants. They were frequency-matched to cases for sex, ethnicity, and 10-year age category with a ratio of 1.5 controls per case. The 506 cases (333 males and 173 females) and 771 controls (499 males and 272 females) were interviewed, with a nonresponse rate of 11% for cases. Next of kin provided interviews for 50% and 43% of male and female cases, respectively. Among controls, only 2% of the interviews were provided by next of kin for each sex. Data were collected by personal interviews conducted by bilingual interviewers in the participants' homes. A lifetime occupational history and a self-reported history of exposure to specific agents were obtained for each job held for at least 6 months since age 12. Questions were asked about the title of the position, duties performed, location and nature of industry, and time at each job title. A detailed smoking history was also obtained. The variables on occupational exposures were coded according to the Standard Industrial Classification scheme by a single person and reviewed by another. To test the hypothesis about the high-risk jobs for lung cancer, an a priori listing of suspected occupations and industries was created by a two-step process involving a literature review for implicated industries and occupations by the principal investigator. The appropriate Standard Industrial Classification and Standard Occupational Codes associated with job titles were also determined by the principal investigator. For four agents—asbestos, wood dust, diesel exhaust, and formaldehyde—the industries and occupations determined to have exposure were identified, and linking of specific industries and occupations was based on literature review and consultation with local industrial hygienists.

The relative odds were calculated for suspect occupations and industries, classifying individuals as ever employed for at least 1 year in an industry or occupation and defining the reference group as those subjects never employed in that particular industry or occupation. Multiple logistic regression models were used to control simultaneously for age, ethnicity, and smoking status. For occupations with potential diesel exhaust exposure, the analysis showed no excess risks for diesel engine mechanics and auto mechanics. Similarly, when analyzed by exposure to specific agents, the odds ratio adjusted for age, smoking, and ethnicity was not elevated for diesel exhaust fumes (OR = 0.6, 95% CI = 0.2, 1.6). Elevated odds ratios were found for uranium miners (OR = 2.8, 95% CI = 1.0, 7.7), underground miners (OR = 2.4, 95% CI = 1.2, 4.4), construction painters (OR = 2.4, 95% CI = 0.6, 9.6), and welders (OR = 4.3, 95% CI = 1.6, 11.0). No excess risks were detected for the following industries: shipbuilding, petroleum refining, construction, printing, blast furnace, and steel mills; or for the following occupations: construction workers, painters, plumbers, paving equipment operators, roofers, engineers and firemen, woodworkers, and shipyard workers. Females were excluded from detailed analysis because none of the Hispanic female controls had been employed in high-risk jobs; among the non-Hispanic white controls, employment in a high-risk job was recorded for at least five controls for only two industries, construction and painting, for which the odds ratios were not significantly elevated. Therefore, the analyses were presented for males only.

Among the many strengths of this study are its population-based design, high participation rate, detailed smoking history, and the separate analysis done for the two ethnic groups, southwestern Hispanic and non-Hispanic white males. The major limitations pertain to the occupational exposure date. Job titles obtained from occupational histories were used as proxy for exposure status, but these were not validated. Further, for nearly half the cases, next of kin provided occupational histories. The authors acknowledge the above sources of bias but state without substantiation that these biases would not strongly affect their results. They also did not use a job exposure matrix to link occupations to exposures and did not provide details on the method they used to classify individuals as diesel exhaust exposed based on reported occupations. The observed absence of an association for exposure to asbestos, a well-established lung carcinogen, may be explained by the misclassification errors in exposure status or by sample size constraints (not enough power). Likewise, the association for diesel exhaust reported by only 7 cases and 17 controls also may have gone undetected because of low power. In conclusion, there is insufficient evidence from this study to confirm or refute an association between lung cancer and diesel exhaust exposure.

8.3.5. Garshick et al. (1987): A Case-Control Study of Lung Cancer and Diesel Exhaust Exposure in Railroad Workers

An earlier pilot study of the mortality of railroad workers by the same investigators (Schenker et al., 1984) found a moderately high risk of lung cancer among the workers who were exposed to diesel exhaust as compared to those who were not. This study was designed to evaluate the feasibility of conducting a large retrospective cohort study. On the basis of these findings the investigators conducted a case-control study of lung cancer in the same population. The population base for this case-control study was approximately 650,000 active and retired male U.S. railroad workers with 10 years or more of railroad service who were born in 1900 or later. The U.S. Railroad Retirement Board (RRB), which operates the retirement system, is separate from the Social Security System, and to qualify for the retirement or survivor benefits the workers had to acquire 10 years or more of service. Information on deaths that occurred between March 1, 1981, and February 28, 1982, was obtained from the RRB. For 75% of the deceased population, death certificates were obtained from the RRB, and, for the remaining 25%, they were obtained from the appropriate state departments of health. Cause of death was coded according to the eighth revision of the ICD. The cases were selected from deaths with primary lung cancer, which was the underlying cause of death in most cases. Each case was matched to two deceased controls whose dates of birth were within 2.5 years of the date of birth of the case and whose dates of death were within 31 days of the date of death noted in the case. Controls were then selected randomly from workers who did not have cancer noted anywhere on their death certificates and who did not die of suicide or of accidental or unknown causes.

Each subject's work history was determined from a yearly job report filed by his employer with the RRB from 1959 until death or retirement. The year 1959 was chosen as the effective start of diesel exhaust exposure for this study, since by this time 95% of the locomotives in the United States were diesel powered. Investigators acknowledge that because the transition to diesel-powered engines took place in the early 1950s, some workers had additional exposure prior to 1959; however, if a worker had died or retired prior to 1959, he was considered unexposed. Exposure to diesel exhaust was considered to be dichotomous for this study, which was assigned based on an industrial hygiene evaluation of jobs and work areas. Selected jobs with and without regular diesel exhaust exposure were identified by a review of job title and duties. Personal exposure was assessed in 39 job categories representative of workers with and without diesel exhaust exposure. Those jobs for which no personal sampling was done were considered exposed or unexposed on the basis of similarities in job activities and work locations and by degree of contact with diesel equipment. Asbestos exposure was categorized on the basis of jobs held in 1959, or on the last job held if the subject retired before 1959. Asbestos exposure in railroads occurred primarily during the steam engine era and was related mostly to the repair of locomotive

steam boilers that were insulated with asbestos. Smoking history information was obtained from the next of kin.

Death certificates were obtained for approximately 87% of the 15,059 deaths reported by the RRB, from which 1,374 cases of lung cancer were identified. Fifty-five cases of lung cancer were excluded from the study for either incomplete data (20) or refusal by two States to use information on death certificates to contact the next of kin. Successful matching to at least one control with work histories was achieved for 335 (96%) cases ≤64 years of age at death and 921 (95%) cases ≥65 years of age at death. In both age groups, 90% of the cases were matched with two controls. There were 2,385 controls in the study, 98% were matched within ±31 days of the date of death, whereas the remaining 2% were matched within 100 days. Deaths from diseases of the circulatory system predominated among controls. Among the younger workers, approximately 60% had exposure to diesel exhaust, whereas among older workers, only 47% were exposed to diesel exhaust.

Analysis by a regression model, in which years of diesel exhaust exposure were the sum total of the number of years in diesel-exposed jobs, used as a continuous exposure variable, yielded an odds ratio of lung cancer of 1.39 (95% CI = 1.05, 1.83) for over 20 years of diesel exhaust exposure in the ≤64 years of age group. After adjustment for asbestos exposure and lifetime smoking (pack-years), the odds ratio was 1.41 (95% CI = 1.06, 1.88). Both crude odds ratio and asbestos exposure as well as lifetime smoking adjusted odds ratio for the ≥65 years of age group were not significant. Increasing years of diesel exhaust exposure, categorized as ≥20 diesel years and 5 to 19 diesel years, with 0 to 4 years as the referent group, showed significantly increased risk in the ≤64 years of age group after adjusting for asbestos exposure and pack-year category of smoking. For individuals who had ≥20 years of diesel exhaust exposure, the odds ratio was 1.64 (95% CI = 1.18, 2.29), whereas among individuals who had 5 to 19 years of diesel exhaust exposure, the odds ratio was 1.02 (95% CI = 0.72, 1.45). In the ≥65 years of age group, only 3% of the workers were exposed to diesel exhaust for more than 20 years. Relative odds for 5 to 19 years and ≥20 years of diesel exposure were less than 1 ($p>0.01$) after adjusting for smoking and asbestos exposure.

Alternate models to explain post-asbestos exposure were tested. These were variables for regular and intermittent exposure groups and an estimate of years of exposure based on estimated years worked prior to 1959. No differences in results were seen. The interactions between diesel exhaust exposure and the three pack-year categories (<50, >50, and missing pack-years) were explored. The cross-product terms were not significant. A model was also tested that excluded recent diesel exhaust exposure occurring within the 5 years before death and gave an odds ratio of 1.43 (95% CI = 1.06, 1.94) adjusted for cigarette smoking and asbestos exposure, for workers

with 15 years of cumulative exposure. For workers with 5 to 14 years of cumulative exposure, the relative odds were not significant.

The many strengths of the study are consideration of confounding factors such as asbestos exposure and smoking; classification of diesel exhaust exposures by job titles and industrial hygiene sampling; exploration of interactions between smoking, asbestos exposure, and diesel exhaust exposure; and good ascertainment (87%) of death certificates from the 15,059 deaths reported by the RRB.

The investigators also recognized and reported the following limitations: overestimation of cigarette consumption by surrogate respondents, which may have exaggerated the contribution of smoking to lung cancer risk, and use of the Interstate Commerce Commission (ICC) job classification as a surrogate for exposure, which may have led to misclassification of diesel exhaust exposure jobs with low intensity and intermittent exposure, such as railroad police and bus drivers, as unexposed. These two limitations would result in the underestimation of the lung cancer risk. This source of error could have been avoided if diesel exhaust exposures were categorized by a specific dose range associated with a job title that could have been classified as heavy, medium, low, and zero exposure instead of a dichotomous variable. The use of death certificates to identify cases and controls may have resulted in misclassification. Controls may have had undiagnosed primary lung cancer, and lung cancer cases might have been secondary lesions misdiagnosed as primary lung cancer. However, the investigators quote a third National Cancer Survey report in which the death certificates for lung cancer were coded appropriately in 95% of the cases. Last, as in all previous studies, there is a lack of data on the contribution of unknown occupational or environmental exposures and passive smoking. In conclusion, this study, compared with previous studies (on diesel exposure and lung cancer risk), provides the most valid evidence that occupational diesel exhaust emission exposure increases the risk of lung cancer.

8.3.6. Benhamou et al. (1988): Occupational Risk Factors of Lung Cancer in a French Case-Control Study

This is a case-control study of 1,625 histologically confirmed cases of lung cancer and 3,091 matched controls, conducted in France between 1976 and 1980. This study was part of an international study to investigate the role of smoking and lung cancer. Each case was matched with one or two controls whose diseases were not related to tobacco use, sex, age at diagnosis (±5 years), hospital of admission, or interviewer. Information was obtained from both cases and controls on place of residence since birth, educational level, smoking, and drinking habits. A complete lifetime occupational history was obtained by asking participants to give their

occupations from the most recent to the first. Women were excluded because most of them had listed no occupation. Men who smoked cigars and pipes were excluded because there were very few in this category. Thus, the study was restricted to nonsmokers and cigarette smokers. Cigarette smoking exposure was defined by age at the first cigarette (nonsmokers, $\leq$20 years, or >20 years), daily consumption of cigarettes (nonsmokers, <20 cigarettes a day, and $\geq$20 cigarettes a day), and duration of cigarette smoking (nonsmokers, <35 years, and $\geq$35 years). The data on occupations were coded by a panel of experts according to their own chemical or physical exposure determinations. Occupations were recorded blindly using the International Standard Classification of Occupations. Data on 1,260 cases and 2,084 controls were available for analysis. The remaining 365 cases and 1,007 controls were excluded because they did not satisfy the required smoking status criteria.

A matched logistic regression analysis was performed to estimate the effect of each occupational exposure after adjusting for cigarette status. Matched relative risk (RR) ratios were calculated for each occupation with the baseline category, which consisted of patients who had never been engaged in that particular occupation. The matched relative risk ratios adjusted for cigarette smoking for the major groups of occupations showed that the risks were significantly higher for production and related workers, transport equipment operators, and laborers (RR = 1.24, 95% CI = 1.04, 1.47). On further analysis of this group, for occupations with potential diesel emission exposure, significant excess risks were found for motor vehicle drivers (RR = 1.42, 95% CI = 1.07, 1.89) and transport equipment operators (RR = 1.35, 95% CI = 1.05, 1.75). No interaction with smoking status was found in any of the occupations. The only other significant excess was observed for miners and quarrymen (RR = 2.14, 95% CI = 1.07, 4.31). None of the significant associations showed a dose-response relationship with duration of exposure.

This study was designed primarily to investigate the relationship between smoking (not occupations or environmental exposures) and lung cancer. Although an attempt was made to obtain complete occupational histories, the authors did not clarify whether, in the logistic regression analysis, they used the subjects' first occupation, predominant occupation, last occupation, or ever worked in that occupation as the risk factor of interest. The most important limitation of this study is that the occupations were not coded into exposures for different chemical and physical agents, thus precluding the calculation of relative risks for diesel exposure. Using occupations as surrogate measures of diesel exposure, an excess significant risk was obtained for motor vehicle drivers and transport equipment operators, but not for motor mechanics. However, it is not known if subjects in these occupations worked with diesel engines or nondiesel engines.

8.3.7. Hayes et al. (1989): Lung Cancer in Motor Exhaust-Related Occupations

This study reports the findings from an analysis of pooled data from three lung cancer case-control studies that examine in detail the association between employment in motor exhaust-related (MER) occupations and lung cancer risk adjusted for confounding by smoking and other risk factors. The three studies were carried out by the National Cancer Institute in Florida (1976 to 1979), New Jersey (1980 to 1981), and Louisiana (1979 to 1983). These three studies were selected because the combined group would provide a sufficient sample to detect a risk of lung cancer in excess of 50% among workers in MER occupations. The analyses were restricted to males who had given occupational history. The Florida study was hospital based, with cases ascertained through death certificates. Controls were randomly selected from hospital records and death certificates, excluding psychiatric diseases, matched by age and county. The New Jersey study was population based, with cases ascertained through hospital records, cancer registry, and death certificates. Controls were selected from among the pool of New Jersey licensed drivers and death certificates. The Louisiana study was hospital based (it is not specified how the cases were ascertained), and controls were randomly selected from hospital patients, excluding those with lung diseases and tobacco-related cancers.

A total of 2,291 cases of male lung cancers and 2,570 controls were eligible, and the data on occupations were collected by next-of-kin interviews for all jobs held for 6 months or more, including the industry, occupation, and number of years employed. The proportion of next-of-kin interviews varied by site between 50% in Louisiana to 85% in Florida. The coding schemes were reviewed to identify MER occupations, which included truck drivers and heavy equipment operators (cranes, bulldozers, and graders); bus drivers, taxi drivers, chauffeurs, and other motor vehicle drivers; and automobile and truck mechanics. Truck drivers were classified as routemen and delivery men and other truck drivers. All jobs were also classified with respect to potential exposure to known and suspected lung carcinogens. Odds ratios were calculated by the maximum likelihood method adjusting for age by birth year, usual amount smoked, and study area. Logistic regression models were used to examine the interrelationship of multiple variables.

A statistically significant excess risk was detected for employment of 10 years or more for all MER occupations (except truck drivers) adjusted for birth cohort, usual daily cigarette use, and study area. The odds ratio for lung cancer using data gathered by direct interviews was 1.4 (95% CI = 1.1, 2.0), allowing for multiple MER employment, and 2.0 (95% CI = 1.3, 3.0), excluding individuals with multiple MER employment. Odds ratios for all MER employment, except truck drivers who were employed for less than 10 years, were 1.3 (95% CI = 1.0, 1.7) and 1.3 (95% CI = 0.9, 1.8) including and excluding multiple MER employment, respectively. Odds ratios were then derived for specific MER occupations and, to avoid the confounding effects of multiple MER job classifications, analyses were also done excluding subjects with multiple MER

job exposures. Truck drivers employed for more than 10 years had an odds ratio of 1.5 (95% CI = 1.1, 1.9). A similar figure was obtained excluding subjects with multiple MER employment. An excess risk was not detected for truck drivers employed less than 10 years. The only other job category that showed a statistically significant excess for lung cancer was the one that included taxi drivers and chauffeurs who worked multiple MER jobs for less than 10 years (OR = 2.5, 95% CI = 1.4, 4.8). For the same category, the risk for individuals working in that job for more than 10 years was 1.2 (95% CI = 0.5, 2.6). A statistical significant positive trend ($p<0.05$) with increasing employment of <2 years, 2 to 9 years, 10 to 19 years, and 20+ years was observed for truck drivers but not for other MER occupations. A statistically nonsignificant excess risk was also observed for heavy equipment operators, bus drivers, taxi drivers and chauffeurs, and mechanics employed for 10 years or more. All of the above-mentioned odds ratios were derived adjusted for birth cohort, usual daily cigarette use, and State of residence. Exposure to other occupational suspect lung carcinogens did not account for the excess risks detected.

Results of this large study provide evidence that workers in MER jobs are at an excess risk of lung cancer that is not explained by their smoking habits or exposures to other lung cancers. Because no information on type of engine had been collected, it was not possible to determine if the excess risk was due to exposure to diesel exhaust or gasoline exhaust or the mixture of the two. Among the study's limitations are possible bias due to misclassification of jobs reported by the large proportion of next-of-kin interviews and the problems in classifying individuals into uniform occupational groups based on the pooled data in the three studies that used different occupational classification schemes.

8.3.8. Steenland et al. (1990): A Case-Control Study of Lung Cancer and Truck Driving in the Teamsters Union

Steenland et al. conducted a case-control study of lung cancer deaths in the Teamsters Union to determine the risk of lung cancer among different occupations. Death certificates were obtained from the Teamsters Union files in the central States for 10,485 (98%) male decedents who had filed claims for pension benefits and who had died in 1982 and 1983. Individuals were required to have 20 years tenure in the union to be eligible to claim benefits. Cases comprised all deaths (n = 1,288) from lung cancer, coded as ICD 162 or 163 for underlying or contributory cause on the death certificate. The 1,452 controls comprised every sixth death from the entire file, excluding deaths from lung cancer, bladder cancer, and motor vehicle accidents. Detailed information on work history and potential confounders such as smoking, diet, and asbestos exposure was obtained by questionnaire. Seventy-six percent of the interviews were provided by spouses and the remainder by some other next of kin. The response rate was 82% for cases and 80% for controls. Using these interview data and the 1980 census occupation and industry codes,

subjects were classified either as nonexposed or as having held other jobs with potential diesel exhaust exposure. Data on job categories were missing for 12% of the study subjects. A second work history file was also created based on the Teamsters Union pension application that lists occupation, employer, and dates of employment. A three-digit U.S. census code for occupation and industry was assigned to each job for each individual. This Teamsters Union work history file did not have information on whether men drove diesel or gasoline trucks, and the four principal occupations were long-haul drivers, short-haul or city drivers, truck mechanics, and dock workers. Subjects were assigned the job category in which they had worked the longest.

The case-control analysis was done using unconditional logistic regression. Separate analyses were conducted for work histories from the Teamsters Union pension file and from next-of-kin interviews. Covariate data were obtained from next-of-kin interviews. Analyses were also performed for two time periods: employment after 1959 and employment after 1964. These two cut-off years reflect years of presumed dieselization; 1960 for most trucking companies and 1965 for independent driver and nontrucking firms. Data for analysis could be obtained for 994 cases and 1,085 controls using Teamsters Union work history and for 872 cases and 957 controls using next-of-kin work history. When exposure was considered as a dichotomous variable, for both Teamsters Union and next-of-kin work history, no single job category had an elevated risk. From the next-of-kin data, diesel truck drivers had an odds ratio of 1.42 (95% CI = 0.74, 2.47) and diesel truck mechanics had an odds ratio of 1.35 (95% CI = 0.74, 2.47). Odds ratios by duration of employment as a categorical variable were then estimated. For the Teamsters Union work history data and when only employment after 1959 was considered, both long-haul ($p<0.04$) and short-haul drivers (not significant) showed an increase in risk with increased years of exposure. The length of employment categories for which the trends were analyzed were 1 to 11 years, 12 to 17 years, and 18 years or more. Using 1964 as the cutoff date, long-haul drivers continued to show a significant positive trend ($p=0.04$), with an odds ratio of 1.64 (95% CI = 1.05, 2.57) for those who worked for 13+ years, the highest category. Short-haul drivers, however, did not show a positive trend when 1964 was used as the cutoff date. Similar trend analysis was done for most next-of-kin data. A marginal increase in risk with increasing duration of employment as a truck driver ($p=0.12$) was observed. For truck drivers who primarily drove diesel trucks for 35 years or longer, the odds ratio for lung cancer was 1.89 (95% CI = 1.04, 3.42). The odds ratio was 1.34 (95% CI = 0.81, 2.22) for gasoline truck drivers and 1.09 (95% CI = 0.44, 2.66) for truck mechanics. No significant interactions between age and diesel exhaust exposure or smoking and diesel exhaust exposure were observed. All the odds ratios were adjusted for age, smoking, and asbestos in addition to various exposure categories.

The authors acknowledge several limitations of this study, which include possible misclassifications of exposure and smoking habits, as information was provided by next of kin;

lack of sufficient latency to observe lung cancer excess; and a small nonexposed group (n = 120). Also, concordance between Teamsters Union and next-of-kin job categories could not be easily evaluated because job categories were defined differently in each data set. No data were available on levels of diesel exposure for the different job categories. Given these limitations, the positive findings of this study are probably underestimated.

8.3.9. Boffetta et al. (1990): Case-Control Study on Occupational Exposure to Diesel Exhaust and Lung Cancer Risk

This is an ongoing (since 1969) case-control study of tobacco-related diseases in 18 hospitals (six U.S. cities). Cases comprise 2,584 males with histologically confirmed primary lung cancers. Sixty-nine cases were matched to one control, whereas 2,515 were matched to two controls. Controls were individuals who were diagnosed with non-tobacco-related diseases. The matching was done for sex, age (±2 years), hospital, and year of interview. The interviews were conducted at the hospitals at the time of diagnosis. In 1985, the occupational section of the questionnaire was modified to include the usual occupation and up to five other jobs as well as duration (in years) worked in those jobs. After 1985, information was also obtained on exposure to 45 groups of chemicals, including diesel exhaust at the workplace or during hobby activities. A priori aggregation of occupations was categorized into low probability of diesel exhaust exposure (reference group), possible exposure (19 occupations), and probable exposure (13 occupations). Analysis was conducted based on "usual occupation" on all study subjects, and any occupation with sufficient cases was eligible for further analysis. In addition, cases enrolled after 1985 for which there were self-reported diesel exhaust exposure and detailed work histories were also analyzed separately.

Both matched and unmatched analyses were done by calculating the adjusted (for smoking and education) relative odds using the Mantel-Haenzael method and calculating the test-based 95% confidence interval using the Miettinen method. Unconditional logistic regression was used to adjust for potential confounders (the PROC LOGIST of SAS). Linear trends for risk were also tested according to Mantel.

Adjusted relative odds for possible and probable exposure groups as well as the truck drivers were slightly below unity, none being statistically significant for the entire study population. Although slight excesses were observed for the self-reported diesel exhaust exposure group and the subset of post-1985 enrollees for highest duration of exposure (for self-reported exposure, occupations with probable exposure and for truck drivers), none was statistically significant. Trend tests for the risk of lung cancer among self-reported diesel exhaust exposure, probable exposure, and truck drivers with increasing exposure (duration of exposure used as

surrogate for increasing dose) were nonsignificant too. Statistically significant lung cancer excesses were observed for cigarette smoking only.

The major strength of this study is availability of detailed smoking history. Even though detailed information was obtained for the usual and five other occupations (1985), no effort was made to estimate or verify the actual exposure to diesel exhaust; instead, duration of employment was used as a surrogate for dose. The numbers of cases and controls were large; however, the number of individuals exposed to diesel exhaust was relatively few, thus reducing the power of the study. This study did not attempt latency analysis either. Given these limitations, the findings of this study are unable to provide either positive or negative evidence for a causal association between diesel exhaust and occurrence of lung cancer.

8.3.10. Emmelin et al. (1993): Diesel Exhaust Exposure and Smoking: A Case-Referent Study of Lung Cancer Among Swedish Dock Workers

This is a case-control study of lung cancer drawn from the cohort defined as all-male workers who had been employed as dock workers for at least 6 months between 1950 and 1974. In the population of 6,573 from 20 ports, there were 90 lung cancer deaths (cases), identified through Swedish death and cancer registers, during the period of 1960 to 1982. Of these 90 deaths, the 54 who were workers at the 15 ports for which exposure surrogate information was available were chosen for the case-control study. Four controls, matched on port and age, were chosen for each case from the remaining cohort who had survived to the time of diagnosis of the case. Both live and deceased controls were included. The final analyses were done on 50 cases and 154 controls who had complete information on employment dates and smoking data. The smoking strata were created by classifying ex-smokers as nonsmokers if they had not smoked for at least 5 years prior to the date of diagnosis of the case; otherwise they were classified as smokers.

Relative odds and regression coefficients were calculated using conditional logistic regression models. Comparisons were made both with and without smoking included as a variable, and the possible interaction between smoking and diesel exhaust was tested. Both weighted linear regressions of the adjusted relative odds, and the regression coefficients were used to test mortality trends with all three exposure variables.

Exposure to diesel exhaust was assessed indirectly by initially measuring (1) exposure intensity based on exhaust emission, (2) characteristics of the environment in terms of ventilation, and (3) measures of proportion of time in higher exposed jobs. For exhaust emissions, annual diesel fuel consumption at a port was used as the surrogate. For ventilation, the annual proportion of ships with closed or semiclosed holds was used as the surrogate. The proportion of time spent below decks was used as the surrogate for more exposed jobs. Although data were

collected for all three measures, only the annual fuel consumption was used for analysis. Because every man was likely to rotate through the various jobs, the authors thought using annual consumption of diesel fuel was the appropriate measure of exposure. Consequently, in a second analysis, the annual fuel consumption was divided by the number of employees in the same port that year to come up with the fuel-per-person measure, which was further used to create a second measure, "exposed time." The "annual fuel" and exposed-time data were entered in a calendar time-exposure matrix for each port, from which individual exposure measures were created. A third measure, "machine time" (years of employment from first exposure), was also used to compare the results with other studies. All exposure measures were accumulated from the first year of employment or first year of diesel machine use, whichever came later. The last year of exposure was fixed at 1979. All exposures within 2 years prior to the date of lung cancer diagnosis were omitted from both cases and matched controls. A priori classification into three categories of low, medium, and high exposure was done for all three exposure variables, machine time, fuel, and exposed time.

Conditional logistic regression models, adjusting for smoking status and using low exposures and/or nonsmokers as a comparison group, yielded positive trends for all exposure measures, but no trend test results were reported, and only the relative odds for the exposed-time exposure measure in the high-exposure group (OR = 6.8, 90% CI = 1.3 to 34.9) was reported as statistically significant. For smokers, adjusting for diesel exhaust exposure level, the relative odds were statistically significant and about equal for all the three exposure variables—machine time, OR = 5.7 (90% CI = 2.4 to 13.3); fuel, OR = 5.5 (90% CI = 2.4 to 12.7); and exposed time, OR = 6.2 (90% CI = 2.6 to 14.6). Interaction between diesel exhaust and smoking was tested by conditional logistic regression in the exposed-time variable. Although there were positive trends for both smokers and nonsmokers, the trend for smokers was much steeper—low, OR = 3.7 (90% CI = 0.9 to 14.6); medium, OR = 10.7 (90% CI = 1.5 to 78.4); and high, OR = 28.9 (90% CI = 3.5 to 240)—indicating more than additive interaction between these two variables.

In the weighted linear regression model with the exposed-time variable, the results were similar to those using the logistic regression model. The authors also explored the smoking variable further in various analyses, some of which suggested a strong interaction between diesel exhaust and smoking. However, with just six nonsmokers and no further categorization of smoking amount or duration, these results are of limited value.

The diesel exhaust exposure matrices created using three different variables are intricate. Analyses by any of these variables essentially yield the same positive results and positive trends, providing consistent support for a real effect of diesel exhaust exposure, at least in smokers. However, there are some methodological limitations to this study that prevent a more definitive conclusion. The numbers of cases and controls are small. There are very few nonsmokers, thus

testing the effects of diesel exhaust exposure in them is futile. Lack of information on asbestos exposure, to which dock workers are usually exposed, may also confound the results. Also, no latency analyses are presented. Overall, despite these limitations, this study supports the earlier findings of excess lung cancer mortality among individuals exposed to diesel exhaust.

Table 8-2 summarizes the above lung cancer case-control studies.

8.4. CASE-CONTROL STUDIES OF BLADDER CANCER

8.4.1. Howe et al. (1980): Tobacco Use, Occupation, Coffee, Various Nutrients, and Bladder Cancer

This is a Canadian population-based case-control study conducted in the provinces of British Columbia, Newfoundland, and Nova Scotia. These areas were selected because they had cancer registries and were believed not to have concentrations of high-risk industries. All patients with newly diagnosed bladder cancer occurring in the three provinces between April 1974 and June 1976 were identified, and 77% of them were interviewed at home. A total of 480 male and 152 female case-control pairs were available for analysis. For each case, one neighborhood control, matched by age (±5 years) and sex, was also interviewed at home to obtain data on smoking, occupation, dietary sources of nitrites and nitrates that convert to

Table 8-2. Epidemiologic studies of the health effects of exposure to diesel exhaust: case-control studies of lung cancer

Authors	Population studied	Diesel exhaust exposure assessment	Results	Limitations
Williams et al. (1977)	7,518 (3,539 males and 3,979 females) incident invasive cancers from the Third National Cancer Survey Lung cancer cases: 32 in males 28 in females Combined other cancer sites were used as controls	Main lifetime, recent, and other employment information obtained at the time of survey 1970 Census Coding Scheme for Employment was used to code the occupations by one of the authors	SNS elevated relative odds were observed among occupations of trucking, railroading, and mining	Exposure estimation based on self-report that was not validated 47% nonresponse Control group consisted of other cancers, probably diluting the risk estimation Small numbers in cause-specific cancers and individual occupations
Hall and Wynder (1984)	502 histologically confirmed lung cancers Cases diagnosed 12 mo prior to interviews 502 matched hospital controls without tobacco-related diseases, matched for age, sex, race, and geographical area Population from 18 hospitals in controls	Based on previous Industrial Hygiene Standards for a particular occupation, usual lifetime occupation coded as “probably high exposure” and “no exposure” NIOSH standards used to classify exposures: High Moderate Low	SNS excess risk after adjustment for smoking for lung cancer: RR = 1.4 (1st criteria) and RR = 1.7 (NIOSH criteria)	Complete lifetime employment history not available Self-reported occupation history not validated No analysis by dose, latency, or duration of exposure No information on nonoccupational diesel exposure

Table 8-2. Epidemiologic studies of the health effects of exposure to diesel exhaust: case-control studies of lung cancer (continued)

Authors	Population studied	Diesel exhaust exposure assessment	Results	Limitations
Damber and Larsson (1987)	589 lung cancer cases who had died prior to 1979 reported to Swedish registry between 1972 and 1977 582 matched dead controls (sex, age, year of death, municipality) drawn from National Registry of Cause of Death 453 matched living controls (sex, year of birth, municipality) drawn from National Population Registry	Occupations held for at least 1 year or more Using a 5-digit code the occupations were classified according to Nordic Classification of Occupations	SS OR = 2.7 (≥1 year of employment) SS OR = 9.8 (≥20 years of employment) Adjustment for smoking was done SNS OR = 1.2 for professional drivers (≥20 years of employment) with dead controls SNS OR = 1.1 ≥20 years of employment) with living controls	Uncertain diesel exhaust exposure No validation of exposure done Underground miners data not adjusted for other confounders such as radon, etc.
Lerchen et al. (1987)	506 lung cancer cases from New Mexico tumor registry (333 males and 173 females) Aged 25-84 years Diagnosed between January 1, 1980, and December 31, 1982 771 (499 males and 272 females) frequency matched with cases, selected from telephone directory	Lifetime occupational history and self-reported exposure history were obtained Coded according to Standard Industrial Classification Scheme	No excess of relative odds was observed for diesel exhaust exposure	Exposure based on occupational history and self-report, which was not validated 50% occupational history provided by next of kin Absence of lung cancer association with asbestos suggests misclassification of exposure
Garshick et al. (1987)	1,319 lung cancer cases who died between March 1, 1981, and February 28, 1982 2,385 matched controls (two each, age and date of death) Both cases and controls drawn from railroad worker cohort who had worked for 10 or more years	Personal exposure assessed for 39 job categories This was corrected with job titles to dichotomize the exposure into: Exposed Not exposed	SS OR = 1.41 (≤64 year age group) SS OR = 1.64 (≤64 year age group) for ≥20 years diesel exhaust exposure group when compared to 0- to 4-year exposure group All ORs adjusted for lifetime smoking and asbestos exposure	Probable misclassification of diesel exhaust exposure jobs Years of exposure used as surrogate for dose 13% of death certificates not ascertained Overestimation of smoking history

Table 8-2. Epidemiologic studies of the health effects of exposure to diesel exhaust: case-control studies of lung cancer (continued)

Authors	Population studied	Diesel exhaust exposure assessment	Results	Limitations
Benhamou et al. (1988)	1,260 histologically confirmed lung cancer cases 2,084 non-tobacco-related disease matched controls (sex, age at diagnosis, hospital admission, and interviewer) Occurring between 1976 and 1980 in France	Based on exposures determined by panel of experts The occupations were recorded blindly using International Standard Classification of Occupations as chemical or physical exposures	Significant excess risks were found in motor vehicle drivers (RR = 1.42) and transport equipment operators (RR = 1.35) (smoking adjusted)	Exposure based on occupational histories not validated Exposures classified as chemical and physical exposure, not specific to diesel exhaust
Hayes et al. (1989)	Pooled data from three different studies consisting of 2,291 male lung cancer cases 2,570 controls	Occupational information from next of kin for all jobs held Jobs classified with respect to potential exposure to known and suspected pulmonary carcinogens	SS OR = 1.5 for truck drivers (>10 years of employment) SS positive trend with increasing employment as truck driver	Exposure data based on job description given by next of kin, which was not validated Could have been mixed exposure to both diesel and gasoline exhausts Job description could have led to misclassification
Steenland et al. (1990)	1,058 male lung cancer deaths between 1982 and 1983 1,160 every sixth death from entire mortality file sorted by social security number (excluding lung cancer, bladder cancer, and motor vehicle accidents) Cases and controls were from Central State Teamsters who had filed claims (requiring 20-year tenure).	Longest job held: diesel truck driver, gasoline truck driver, both types of trucks, truck mechanic, and dock workers	As 1964 cut-off point: SS OR = 1.64 for long-haul drivers with 13+ years of employment Positive trend test for long-haul drivers (p=0.04) SS OR = 1.89 for diesel truck drivers of 35+ years of employment	Exposure based on job titles not validated Possible misclassification of exposure and smoking, based on next-of-kin information Lack of sufficient latency

Table 8-2. Epidemiologic studies of the health effects of exposure to diesel exhaust: case-control studies of lung cancer (continued)

Authors	Population studied	Diesel exhaust exposure assessment	Results	Limitations
Boffetta et al. (1990)	From 18 hospitals (since 1969) 2,584 male lung cancer cases matched to either one control (69) or two controls (2,515) were drawn. Matched on age, hospital, and year of interview	A priori aggregation of occupations categorized into low probability, possible exposure (19 occupations), and probable exposure (13 occupations) to diesel exhaust	OR slightly below unity SNS	No verification of exposure Duration of employment used as surrogate for dose Number of individuals exposed to diesel exhaust was small
Emmelin et al. (1993)	50 male lung cancer cases from 15 ports (worked for at least 6 months between 1950 and 1974), 154 controls matched on age and port	Indirect diesel exhaust exposure assessment done based on (1) exposure intensity, (2) characteristics of ventilation, (3) measure of proportion of time in higher exposure jobs	SS OR for high-exposure group = 6.8	Numbers of cases and controls are small Very few nonsmokers Lack of exposure information on asbestos No latency analysis

Abbreviations: OR = odds ratio; RR = relative risk; SNS = statistically nonsignificant; SS = statistically significant.

nitrosamines (nonpublic water supply and preserved meat products), and beverage consumption, including a detailed history of coffee consumption. A detailed smoking history was obtained. The occupational history included a chronological account of all jobs and the number of years and months during which the respondent had worked in each job, experience in industries that were suspected a priori to increase the risk of bladder cancer, and exposure to any jobs that involved exposure to dust and fumes at the workplace. Relative risk estimates were computed using the linear logistic model applied to individually matched case-control pairs.

A baseline comparison of cases and controls showed that, whereas male patients were similar to controls on income and education, there was an excess of female cases with low family incomes and low levels of educational attainment. For both sexes, the mean ages for cases and controls did not differ, and the times required for the interview were similar. An analysis by the a priori suspect industries showed elevated risks for a number of industries for males. These included the chemical (RR = 7.5, 95% CI = 1.7, 67.6), rubber (RR = 5.0, 95% CI = 0.6, 236.5), petroleum (RR = 5.3, 95% CI = 1.5, 28.6), medicine (RR = 2.6, 95% CI = 0.9, 9.3), and spray painting (RR = 1.8, 95% CI = 0.7, 4.6) industries. The excess risks were statistically significant only for the petroleum and chemical industries. The estimates did not change when the analysis was done separately for subjects who reported only one exposure and for those who reported exposure to more than one suspect industry. The estimates also remained unchanged after controlling for smoking. Too few females reported working in the a priori suspect industries to make any meaningful contribution to the analysis. Among males, statistically nonsignificant excess risks were observed for tanning, electric cable, photographic, commercial paint, tailoring, medicine, food processing, and agricultural industries. The analysis by exposure to dust and fumes in occupations other than those in the a priori suspect list detected the relative risks for diesel and traffic fumes (RR = 2.8, 95% CI = 0.8, 11.8). Statistically significant excess risks were observed for railroad workers (RR = 9.0, 95% CI = 1.2, 394.5) and welders (RR = 2.8, 95% CI = 1.1, 8.8). For occupations other than those on the a priori list for males and females, statistically significant excesses were detected for metal machinists (RR = 2.7, 95% CI = 1.1, 7.6), metal recorders (RR = 2.6, 95% CI = 1.0, 7.3), and nursery men (RR = 5.5, 95% CI = 1.2, 51.1). Statistically nonsignificant excesses were also detected for exposure to two chemicals: benzidine and its salts, RR = 1.3, and *bis*-chloromethyl ether, RR = 5.0. A detailed analysis was done for cigarette smoking, which demonstrated statistically significant increasing bladder cancer risk with increasing duration of smoking, total lifetime consumption of packs of cigarettes, and average frequency of cigarettes per day. In males the highest significant risk was observed for latency of less than 35 years; after that time the risk reduced slightly with increasing latency. In females the highest significant risk was for more than 35 years of latency. Risks were elevated for males consuming all types of coffee and for females consuming instant coffee. Hair dye usage in females

and phenacetin usage in males and females carried no risk. Significant risks for use of artificial sweeteners and use of nonpublic water supplies (nitrates and nitrites) were found among males only.

This study was mainly designed to evaluate the various risk factors for bladder cancer such as smoking, coffee consumption, nitrates and nitrites in diet, etc. The major limitation of this study, as the authors noted, was that the three selected provinces did not have high concentrations of industries suspected to be linked to bladder cancer. An excess risk was, however, detected for railroad workers and for those in the "exposed to diesel and traffic fumes category." Risks for those exposed to "diesel fumes only" were not available, nor do we know the exact job title of the railroad workers and the type of engines they were operating. The authors also did not detail the method by which they coded the information given by respondents in response to questions on exposure to dust and fumes into the various categories they used in the analysis. These analyses were done for subjects who reported having "ever been exposed" versus "never been exposed" to these fumes, and although detailed chronological work histories were obtained, no attempt was made to develop a lifetime cumulative exposure index to diesel fumes. In multiple logistic regression models, the authors used the a priori high-risk occupations; hence, nothing can be concluded about exposure to diesel exhaust for occupations that were not part of that list. The authors provided no explanation on possible selection bias, as only 77% of the eligible population was included in the study.

8.4.2. Wynder et al. (1985): A Case-Control Study of Diesel Exhaust Exposure and Bladder Cancer

A case-control study of diesel exhaust exposure and bladder cancer risk was conducted by Wynder et al. (1985). Cases and controls were obtained from 18 hospitals located in six U.S. cities between January 1981 and May 1983. Cases were individuals with histologically confirmed primary cancer of the bladder, diagnosed within 12 months prior to the interview. Controls were individuals with non-tobacco-related diseases who were matched to the cases by age (within 8 years), race, year of interview, and hospital of admission. Women were excluded from the study because the focus was on male-dominated occupations. A structured questionnaire was administered in the hospital to cases and controls to elicit information on usual occupation, smoking history, alcohol and coffee consumption, as well as other demographic factors.

Two methods were used to define occupational exposure to diesel exhaust. First, occupational titles defined by the industrial hygiene standards as probable high exposure were classified as exposed or not exposed to diesel exhaust. The probable high-exposure category consisted of bus and truck drivers, heavy equipment operators and repairmen, railroad workers, and warehousemen. In the second method, guidelines set by NIOSH were used to classify

occupations based on exposure to diesel exhaust. In this method, the estimated proportion of exposed workers was computed for each occupational category by using the NIOSH estimates of the exposed population as the numerator and the estimates of individuals employed in each occupational category from the 1970 census as the denominator. Occupations estimated to have at least 20% of their employees exposed to diesel exhaust were defined as "high exposure," those with 10% to 19% of their employees exposed as "moderate exposure," and those with less than 10% of their employees exposed as "low exposure." The odds ratio was used as a measure of association to assess the relationship between bladder cancer and diesel exhaust exposure. The overall participation among those eligible and available for interview was 75% and 72% in cases and controls, respectively.

A total of 194 bladder cancer cases and 582 controls were examined, and the two groups were found to be comparable by age and education. Except for railroad workers, who had relative odds of 2.0 based on two cases and three controls (95% CI = 0.34, 11.61), the relative odds were less than 1 for other diesel exhaust exposure occupations such as bus and truck drivers, warehousemen, material handlers, and heavy equipment workers. When the risk was examined using the NIOSH criteria for high, moderate, and low exposure, relative odds were 1.68 and 0.16 for high and moderate, respectively, with low as the referent group; neither was statistically significant. Cases and controls were compared by smoking status. Cases were more likely to be current cigarette smokers than were controls. Current smokers of 1 to 20 cigarettes/day had relative odds of 3.64 (95% CI = 2.04, 6.49), current smokers of 21+ cigarettes/day had relative odds of 3.51 (95% CI = 2.00, 6.19), while ex-smokers had relative odds of 1.72 (95% CI = 1.01, 2.92). After controlling for smoking, there was no significant increase in the risk of bladder cancer for occupations with diesel exhaust exposure compared to occupations without diesel exhaust exposure. A synergistic effect between the two also was not detected.

This study has two major methodologic limitations, both pertaining to exposure classification. First, the use of "usual" occupation may have led to misclassification of those individuals who had held a previous job with diesel exhaust exposure that was not their usual occupation; this may have resulted in reduced power to detect weak associations. Second, since there was no information on amount or duration of diesel exhaust exposure, no analysis of dose-response relationships could be done. Also, no information was available on other confounding risk factors of bladder cancer such as urinary retention, amphetamine abuse, and smoking within the confined space of a truck cab, all of which are lifestyle factors specific to the truck-driving occupation.

8.4.3. Hoar and Hoover (1985): Truck Driving and Bladder Cancer Mortality in Rural New England

This study investigated the relationship between the occupation of truck driving and bladder cancer mortality in a case-control study in New Hampshire and Vermont. Cases included all white residents of New Hampshire and Vermont who died from bladder cancer (eighth revision of the ICD) between 1975 and 1979. Death certificates were provided by the vital records and health statistics office of the two States, and the next of kin were traced and interviewed in person. Two types of controls were selected for each case. One control was randomly selected from all other deaths, excluding suicides, and matched on State, sex, race, age (±2 years), and year of death. The second for control was selected with the additional matching criteria of county of residence. Completed interviews were obtained from 325 (out of 410) next of kin for cases and 673 (out of 923) for controls. Information on demographic characteristics, lifetime occupational and residential histories, tobacco use, diet, and medical history was obtained on each subject. The odds ratio was calculated to ascertain a measure of association between truck driving and bladder cancer. Because separate analyses of the two control series gave similar results, the two control series were combined. Also, because matched analyses yielded results similar to those provided by the unmatched analyses, results of the unmatched analyses were presented.

Sixteen percent (35) of the cases and 12% (53) of the controls had been employed as truck drivers, yielding an odds ratio of 1.5 (95% CI = 0.9, 2.6) after adjustment for county of residence and age at death. For New Hampshire, the odds ratio was 1.3 (95% CI = 0.7, 2.3), and for Vermont, the odds ratio was 1.7 (95% CI = 0.8, 3.4). For a large number of subjects, the next of kin were unable to give the durations of truck driving, and there was an inconsistent positive association with years of truck driving. Crude relative odds were not altered after adjustment for coffee drinking, cigarette smoking, and education as a surrogate for social class. Little variation in risks was seen when the data were analyzed by the industry in which the men had driven trucks. No relationship was seen between age at which employment as a truck driver started and occurrence of bladder cancer. Analysis by duration of employment as a truck driver and bladder cancer showed a positive trend of increasing relative odds with increasing duration of employment. The trend test was statistically significant (p=0.006). The odds ratio was statistically significant for the 5 to 9 years of employment category only (OR = 2.9, 95% CI = 1.2, 6.7). Similarly, analysis by calendar year first employed showed a statistically significant odds ratio for 1930 to 1949 (OR = 2.6, 95% CI = 1.3, 5.1), whereas relative odds were not significant if subjects were employed prior to 1929 or after 1950.

The effects of reported diesel exhaust exposure from fuel or engines in truck driving or other occupations were then analyzed. An odds ratio of 1.8 (95% CI = 0.5, 7.0) was derived for

those who were exposed to diesel exhaust during their truck-driving jobs as compared to an odds ratio of 1.5 (95% CI = 0.8, 2.7) for those not reporting diesel exhaust exposure. Analysis by duration of exposure (0, 1 to 19 years, 20 to 29 years, 30 to 39 years, and 40+ years) to diesel fuel or engines in other occupations, which were "self-reported" by participants, showed a statistically significant positive trend (p=0.024) for bladder cancer, although none of the individual odds ratios in these duration categories were statistically significant.

This study investigated an association between truck driving and bladder cancer in an attempt to understand the reasons for the high rates of bladder cancer in rural areas of New Hampshire and Vermont. Although an elevated odds ratio for bladder cancer (not statistically significant) was observed for reported truck-driving occupations, there was insufficient evidence to conclude that the excess risk of bladder cancer was due to exposure to diesel emissions. This is because the excess bladder cancer risk was observed for all truck drivers irrespective of their exposure to diesel emissions. Also, no information was provided on the confounding effects of other aspects of the road environment such as urinary retention, amphetamine abuse, and concentrated cigarette smoke within the truck cab. Other limitations of this study include the use of next of kin for occupational histories, who may either under- or overreport occupations, and the use of death certificates with their inherent problems of misclassification.

8.4.4. Steenland et al. (1987): A Case-Control Study of Bladder Cancer Using City Directories as a Source of Occupational Data

The primary objective of the study was to test the usefulness of city directories as a source of occupational data in epidemiologic studies of illness and occupational exposure. Commercial city directories provide data on occupations and employers and are compiled from a door-to-door yearly census of all residents 18 years old and older. The directories are available in most medium-size cities in the United States. A unique feature of city directory data is that they identify specific employers, and as the authors suggest, this information may be better than death certificates for rapid, inexpensive, record-based epidemiologic studies.

A case-control study was conducted of male bladder cancer deaths in Hamilton County (including Cincinnati), OH. This county was selected because it is in an industrialized area with high bladder cancer rates and also because city directories cover approximately 85% of the people living in the county. A computerized list of all male bladder cancer deaths (n = 731) and all other male deaths (n = 95,057), with the exclusion of deaths from urinary tract tumors and pneumonia, that occurred between 1960 and 1982 was obtained from the Ohio Department of Vital Statistics. Death certificates had been coded by a nosologist according to the ICD code in use at the time of death. A pool of six controls was created for each case matched on sex, residence in Hamilton County at time of death, year of death, age at death (±5 years), and race.

Two types of analysis were performed, one based on city directory data and the other based on death certificate data. In the former, cases and controls were restricted to individuals who had at least one yearly directory listing with some occupational data. The first two controls from the pool of six who met the requirements were selected. This analysis involved 648 cases (627 cases had 2 controls and 21 cases had only 1 control) and 1,275 controls.

The death certificate analysis involved all 731 cancer deaths, with two controls per case. In most cases, the same two controls were used in this analysis too. The usual lifetime occupation and industry on the death certificate was abstracted from them. Data on occupation and industry were coded with a three-digit U.S. census code using the method adopted by the U.S. Bureau of the Census. Five of the occupational data were recorded for occupation and industry by a second coder, with a high degree of reproducibility. Odds ratios were calculated for bladder cancer using a Mantel-Haenszel procedure.

The city directory data identified four employers significantly associated with bladder cancer deaths; only one of them was identified by the death certificate data which provided only lifetime type of industry rather than the name of a specific employer. The industries represented by the four employers were a chemical plant, printing company, valve company, and machinery plant. The city directory data analysis demonstrated significant positive associations for quite a few occupations. The occupations that had at least 10 cases or more were engineers (OR = 3.00, p=0.01), carpenters (OR = 2.36, p<0.01), tailors (OR = 2.56, p<0.01), and furnace operators (OR = 2.5, p=0.03). Relative odds were increased significantly with increased duration of employment ($\geq$20 years) for truck drivers (OR = 12, p=0.01) and furnace operators (based on four cases and no controls, p=0.05). For occupations in which subjects had ever been employed, a significant increase in the relative odds with increased duration of employment was observed for the railroad industry ($\geq$20 years of employment, OR = 2.21, p<0.05). Both truck driving and railroad industry occupations involve diesel emission exposures.

The analysis of death certificate data yielded associations in the same direction for most of the occupations. A check of the validity of city directory data indicated that 77% of the listings agreed with the Social Security earnings report for the employer in any given year. A comparison of city directory and death certificate information on occupations indicated a match for occupation between at least one city directory listing and occupation on death certificates for 68.3% of the study subjects.

This study demonstrated that city directories are a relatively inexpensive and accessible source of occupational data for epidemiologic studies. Limitations of this study include the problem in tracing women because of the change from maiden to married name and the availability of data for only the year of residence in the city. They are superior to death certificates in being able to identify high-risk employers in specific geographic sites. Although

death certificate data reflect usual lifetime occupation, city directories yield data on short-term jobs, some of which may involve critical exposure. Thus, a combination of the two approaches may be most productive in record-based hypothesis-generating studies. The occupational data were missing for 15%, whereas employer data were missing for 36% in the city directory. In the context of the mentioned pros and cons of using city directories, this study found an excess risk for bladder cancer among two occupations with potential diesel exposure: truck drivers and railroad workers. Two sources of bias that may have influenced these findings are selection bias arising from the use of deaths instead of incident cases, because survival for bladder cancer is high, and the absence of data on confounding factors such as smoking, beverage consumption, and medication use.

8.4.5. Iscovich et al. (1987): Tobacco Smoking, Occupational Exposure, and Bladder Cancer in Argentina

This is a hospital-based case-control study of bladder cancer conducted in La Plata, Argentina, to estimate the risk of bladder cancer associated with different types of tobacco, beverages, and occupational exposures. Bladder cancer is one of the most common cancers among males in the La Plata area.

Cases were selected from patients with a histologically confirmed diagnosis of bladder cancer (transitional, squamous-cell, or nonspecific cell type) admitted to the 10 general hospitals in the greater La Plata area (population in 1980 = 580,000) between March 1983 and December 1985. Cases with true bladder papilloma and individuals who were residents of greater La Plata for less than 5 years were excluded. Of the 120 cases eligible to participate, 1 died prior to the interview, 2 refused to participate, and the remaining 117 cases, representing 60% of the incident cases registered in the registry, were interviewed. Two control groups (117 neighborhood and 117 hospital controls) were matched by sex and age (±5 years). Of the 117 cases, 99 were males and 18 were females. Hospital controls, selected from the same hospital as the cases, were hospitalized for the first time within 3 months of diagnosis of the illness of the cases. Twelve percent of the hospital controls had illnesses known to be associated with tobacco smoking. Neighborhood controls were sampled from among persons living in the same block. The interviewer proceeded north in the block where the case resided and selected the first control who met the matching criteria. Seven hospital controls could not be interviewed because of their poor physical health and were replaced. Three neighborhood controls refused to participate and were replaced. Cases and hospital controls were interviewed at the hospital and the neighborhood controls at their homes to collect data on demographic, socioeconomic, and medical variables, detailed smoking habits, and alcoholic and other beverages consumed.

The interviews were done by trained interviewers, two physicians, and a social worker. The cases and hospital controls were interviewed in the hospital by the physicians; hence, the interviews could not be conducted "blind." A detailed occupational history was obtained for the three occupations of longest duration and the most recent one. For each job title, the activity of the plant and type of production were also ascertained. Job titles were coded according to the International Labor Union (ILO) 1970 classification. Plant activity and type of production were coded according to the United Nations 1975 classification categories. Information was also collected on exposure to 33 chemical and physical agents, which included confirmed or suspected bladder carcinogens. A detailed history of smoking habits was also obtained, and individuals were categorized as current smokers if they were smoking at present or if they had stopped smoking less than 2 years previously. Ex-smokers were those who ceased smoking at least for 2 years or more than 2 years previously. For each subject a cumulative lifelong consumption of cigarettes by type was estimated, and an average consumption of cigarettes/day was computed.

Relative risks were computed for occupational factors using the unconditional logistic regression method, adjusting for age and tobacco smoking. These risks were derived for those who were ever employed in that occupation versus those who were never employed in that occupation. Socioeconomic status of cases and neighborhood controls was similar, but there were fewer professionals and more manual workers among hospital controls compared with cases. Occupational variables included job title and type of activity of the plant. Significant excess risks were observed for truck and railroad drivers (RR = 4.31, $p<0.002$) and oil refinery workers (RR = 6.22, $p<0.02$). The risk for truck and railroad drivers was reduced after adjusting for smoking, whereas that for oil refinery workers increased after adjusting for smoking (no RRs were presented). The adjusted relative risks were not reported. A positive but nonsignificant association was observed for printers (RR = 2.6, $p<0.77$).

This study identified smoking and coffee drinking as the major risk factors for bladder cancer in this area. The overall age-adjusted relative risk in males for current smokers relative to nonsmokers was 7.2 (95% CI = 3.0, 20.1), with dose-response relationships observed for the average daily amount as well as for duration of smoking. A strong dose-response relationship was also observed for coffee drinking in males, with a relative risk of 12 (95% CI = 4.3, 33.31) for those drinking more than three cups of coffee per day after adjusting for the effect of smoking. No association was found with use of saccharin in males. No results were presented for females for these risk factors.

This case-control study was conducted primarily to determine the reasons for the high rates of bladder cancer in the La Plata region of Argentina. Only 60% of the cases registered in the cancer registry were interviewed, and no information was provided for the remaining 40% eligible nonrespondents to determine if the study sample was selectively biased in any way. The

sample size of 117 was small, and the analysis of males reduced it to 99. Although the use of two different types of control groups is a strength of this study, none of the interviews were done blind, and it appears that the hospital interviews were done by the physicians and the neighborhood interviews were done by the social worker. Job titles were used as surrogates of exposure, but the authors state that although they attempted to analyze by an exposure index derived from a job exposure matrix (details not provided), they found no difference in exposure between cases and controls. This explanation is ambiguous. The authors also grouped truck and railroad drivers together for reasons not mentioned and did not present separate risk estimates. A table showing the distribution of cases and controls for selected activities or professions did not indicate if the data pertain to both sexes or males only, and the text did not clarify that either. The reported significant excess risks for truck and railroad drivers were reduced after adjusting for smoking, but it was not known if the statistical significance persisted. No analysis was provided for the data collected in the interviews on exposures to the 33 chemical and physical agents, and it was not known if the truck and railroad drivers were operating diesel engines. Although rare in the La Plata area, the occupations known to be associated with bladder cancer (dye, rubber, leather, and textile workers) are acknowledged by the authors.

8.4.6. Iyer et al. (1990): Diesel Exhaust Exposure and Bladder Cancer Risk

This study is a hospital-based case-control study of bladder cancer and potential exposure to diesel exhaust using data from a large ongoing case-control study of tobacco-related neoplasms conducted by the American Health Foundation. An earlier study by Wynder et al. (1985) looked at the relationship between occupational exposure to diesel exhaust and the risk of bladder cancer. For this study, the objective was to evaluate the relationship between the different measures of exposure to diesel exhaust, occupational and self-reported, and the risk of bladder cancer. Cases comprised 136 patients with histologically confirmed primary cancer of the urinary bladder interviewed at 18 hospitals in six U.S. cities. Two controls were selected per case, matched for sex, age (within 2 years), race, hospital, and year of interview. A total of 160 controls had non-tobacco-related malignancies distributed as follows: stomach cancer (6%), colorectal cancer (20%), prostate cancer (6%), and leukemia or lymphoma (8%). Among the 112 controls with nonmalignant diseases, 3% had benign neoplasms, 6% had hyperplasia of the prostate, and 6% had dorsopathies. Distribution of the other nonmalignant illnesses was not provided. Occupational history included information on usual occupation and up to five other jobs. Exposure to diesel exhaust in hobby activities also was collected. For the purpose of this analysis, occupations were aggregated a priori into three categories: low probability of exposure (reference group), possible exposure, and probable exposure. Analyses were also done for self-reported exposure to diesel exhaust. Risk estimates were obtained by unconditional logistic

regression using PROC LOGIST of SAS. Cases and controls were first compared by age, race, education, and smoking habit. Cases were found to be less educated than controls ($p<0.05$). Crude odds ratios for diesel exhaust exposure, based on occupational or self-reported exposure, were not significantly elevated after controlling for smoking and educational status (OR = 1.2, 95% CI = 0.8, 2.0). When individual occupations were analyzed separately, truck drivers showed no excess risk (OR = 0.48, 95% CI = 0.15, 1.56).

The authors concluded that their study does not support the hypothesis of an association between exposure to diesel exhaust and bladder cancer. Several significant limitations of exposure assessment and analysis are evident in this study. In the introduction, the authors stated that they refined the definition of exposure to diesel exhaust by obtaining a lifetime occupational history, but in the methods section they stated that they restricted analysis to usual occupational history and five other jobs, which was not that different from their earlier study (Wynder et al., 1985). The terms, low probability of exposure, possible exposure, and probable exposure, also were not clearly defined. Information on duration of employment or exposure was not presented, and no attempts were made to validate occupational history. No information was available on calendar years of employment in the truck-driving industry or the locomotive occupations. Because diesel trucks and locomotives were introduced in the mid-1950s and the dieselization was completed by 1960, it would be important to use 1960 as a cutoff date and to restrict analysis to subjects who worked in these industries after that date. No information on nonrespondent cases and controls was provided. The authors indicated in the methods section that cases were individually matched to controls, but they performed an unmatched analysis to calculate the odds ratios and did not address why they did not preserve the matching in the analysis, especially because such an analysis could bias the risk estimates to unity.

8.4.7. Steineck et al. (1990): Increased Risk of Urothelial Cancer in Stockholm From 1985 to 1987, After Exposure to Benzene and Exhausts

This study was conducted to investigate the association between benzene, diesel, and petrol exhausts as well as some other industry-related chemicals and the risk of urothelial cancer. Designed as a population-based case-control study, it was conducted among all men born between 1911 and 1945 and living in the County of Stockholm for all or part of the observation period (September 15, 1985, to November 30, 1987). All incident cases of urothelial cancer and squamous-cell carcinoma of the lower urinary tract were contacted for inclusion in the study. Controls were selected by stratified random sampling during the observation period from a computerized register for the population of Stockholm. A postal questionnaire was sent to study subjects at their homes to collect information on occupational history. The questions on occupation included exposure to certain specified occupations/industries/chemicals and lists of all

jobs held and duration in each job. An industrial hygienist, unaware of case-control status, classified subjects as being exposed or unexposed to 38 agents and groups of substances, including 17 exposure categories with aromatic amines. Using all the exposure information, the exposure period was defined and the annual dose was rated as low, moderate, or high based on the accumulated dose (exposure duration multiplied by intensity of exposure) during the course of 1 average year for the defined exposure period. Swedish and international data were used to classify subjects as exposed, based on air concentrations in the work environment that were higher than for the general public, or skin contact with liquids of low volatility. To allow for latency, the authors ignored exposures after 1981. Data were gathered from 256 cases and 287 controls. Controls were selected by stratified random sampling four times from the computerized register during the observation period of the population of the County of Stockholm. These subjects comprised 80% of eligible cases and 79% of eligible controls. Nine of the cases and 16% of the controls refused to participate in the study. The distribution of urothelial cancers was as follows: 5 tumors in the renal pelvis, 243 in the urinary bladder, 5 in the ureter, none in the urethra, and 3 at multiple sites. Two cases who were exposed to a high annual dose of aromatic amines were omitted from all further analysis to eliminate their confounding effects. Crude relative risks were calculated for men classified as exposed or not exposed to several substances. Twenty-five cases and 19 controls reported having been exposed to diesel exhaust, yielding an odds ratio of 1.7 (95% CI = 0.9, 3.3). The corresponding relative odds for petrol exhausts, based on 24 cases and 24 controls, were 1.0 (95% CI = 0.5, 1.9). Odds ratios were then calculated for low, moderate, and high levels of the annual dose adjusted for smoking and year of birth. For diesel exhausts, the odds ratio was 1.3 (95% CI = 0.6, 3.1) for low levels, 2.2 (95% CI = 0.7, 6.6) for moderate levels, and 2.9 (95% CI = 0.3, 30.0) for high levels, indicating a dose response. The corresponding odds ratios for petrol exhausts were 0.6 (95% CI = 0.3, 1.3), 1.4 (95% CI = 0.5, 3.7), and 3.9 (95% CI = 0.4, 35.5). Restricting the analysis to only moderate or high annual doses of exposure adjusted for year of birth and smoking showed a sevenfold increased risk for subjects exposed to both diesel and petrol exhausts (OR = 7.1, 95% CI = 0.9, 58.8). For exposure to diesel (OR = 1.1) and petrol (OR = 1.0) exhausts alone, no excess risk was detected in this analysis. Odds ratios were calculated for low, moderate, and high exposure to benzene, with rates of 1.7 (95% CI = 0.6, 5.1) for low annual doses, 1.1 (95% CI = 0.3, 4.5) for moderate annual doses, and 3.0 (95% CI = 1.0, 8.7) for high annual doses.

The authors discuss misclassification and confounding as sources of bias in this study. To examine misclassification they compared hygienist-assessed exposure and self-reported exposure for printing ink and found a higher relative risk and fewer exposed subjects for hygienist-assessed exposure, indicating that specificity was a problem for self-reported exposure. It is not known to what extent this may have affected the risk estimates for diesel exhausts since data on self-

reported exposure to diesel are not presented. They also mention the possibility of exposure misclassification from using an average annual dose in which a person exposed to an agent at a high level for a few working days and a person exposed to a low level for many days are both rated as exposed to low annual doses. Although statistically nonsignificant elevated odds ratios of 1.3, 2.3, and 2.9 were derived for low, moderate, and high levels of diesel exposure, the authors state that some of their subjects may have later worked in jobs with benzene exposure, and because an elevated risk was detected for benzene exposure, this confounding effect may explain some of the excess risk. An almost statistically significant interaction was observed for exposure to combined diesel and petrol exhausts (OR = 7.1, 95% CI = 0.9, 58.8), which changed to 5.1 (95% CI = 0.6, 43.3) after adjustment for benzene exposure, again providing evidence for the confounding role of benzene exposure in explaining some of the observed results.

Table 8-3 summarizes the bladder cancer case-control studies.

8.5. DISCUSSION AND SUMMARY

Certain extracts of diesel exhaust have been demonstrated to be both mutagenic and carcinogenic in animals and in humans. Animal data suggest that diesel exhaust is a pulmonary carcinogen among rodents exposed by inhalation to high doses over long periods of time. Because large working populations are currently exposed to diesel exhaust and because nonoccupational ambient exposures currently are of concern as well, the possibility that exposure to this complex mixture may be carcinogenic to humans has become an important public health issue.

Table 8-3. Epidemiologic studies of the health effects of exposure to diesel exhaust: case-control studies of bladder cancer

Authors	Population studied	Diesel exhaust exposure assessment	Results	Limitations
Howe et al. (1980)	480 male case-control pairs 152 female case-control pairs Cases diagnosed between April 1974 and June 1976 in three Canadian provinces Matched on age and sex	Based on occupational history of jobs involving exposure to dust and fumes A priori suspect industries	SNS RR = 2.8 for diesel and traffic fumes SS RR = 9.00 for railroad workers	Exposure based on occupational history, which was not validated Diesel exhaust and traffic fumes were combined Only 77% of eligible population included in the study
Wynder et al. (1985)	194 histologically confirmed male cases between the ages of 20 and 80 years 582 matched controls (age, race, year of interview, and hospital of admission); diseases not related to tobacco use From 18 hospitals located in six U.S. cities between January 1981 and May 1983	Occupational titles were defined by Industrial Hygiene Standard into dichotomous “exposed” and “not exposed” Also defined by NIOSH standards into “high exposure,” “moderate exposure,” and “low exposure”	SNS ORs were 1.68 and 0.16 for high and moderate exposure, respectively, as compared to low exposure	Exposure based on usual occupation may have led to misclassification Dichotomous classification made dose-response analysis unattainable No data on other confounders such as smoking

Table 8-3. Epidemiologic studies of the health effects of exposure to diesel exhaust: case-control studies of bladder cancer (continued)

Authors	Population studied	Diesel exhaust exposure assessment	Results	Limitations
Hoar and Hoover (1985)	Population-based, case-control study 325 cases from the residents of New Hampshire and Vermont who died of bladder cancer between 1975 and 1979 A total of 673 controls were chosen from other deaths during the same time period Two matched controls (age, sex, race, state, year of death, and second one matched also on county of residence)	Lifetime occupational history obtained from next of kin	SS OR = 2.9 for 5 to 9 years of employment as truck driver but not for ≥10 years of employment Positive trend (p=0.006) observed with increasing duration of employment as truck driver	Exposure defined as occupation of "truck driver" (i.e., it could have been diesel or gasoline or both) No histological confirmation of bladder cancer diagnosis No data on other confounders such as other exposures, smoking, etc.
Steenland et al. (1987)	648 male bladder cancer deaths from Hamilton County, OH 1,275 matched controls from other deaths (pool of six controls for each case, excluding urinary tract tumors and pneumonias matched on sex, age at death, year of death, race)	Occupation or industry listed in city directory and on death certificates	OR = 12 (p=0.01) for truck drivers with ≥20 years of employment OR = 2.21 ($p \leq 0.05$) for railroad workers with >20 years of employment	Exposure based on city directory or death certificate listing that was not validated Lack of controlling for confounders City directory usually has short-term job listing Missing data on 15% of occupations and 36% for employers in the directory

Table 8-3. Epidemiologic studies of the health effects of exposure to diesel exhaust: case-control studies of bladder cancer (continued)

Authors	Population studied	Diesel exhaust exposure assessment	Results	Limitations
Iscovich et al. (1987)	117 histologically confirmed bladder cancer cases (60% of all incident cases) 117 hospital controls and 117 neighborhood controls (matched on age and sex) Cases and hospital controls from 10 general hospitals in greater La Plata between March 1983 and December 1985	Past and present occupational data were collected by questionnaire An exposure index based on a job exposure matrix was generated	SS OR = 4.3 for truck and railway drivers SS RR = 6.2 for oil refinery workers	Exposure based on job held that was not validated 40% of eligible cases were nonrespondent Small sample size Interviewers were not “blind” to the status of an individual, and this could have biased the findings Truck and railroad drivers were grouped together Not adjusted for other confounding exposures such as dye, rubber, etc.
Iyer et al. (1990)	136 histologically confirmed bladder cancer cases 272 controls, two each matched on sex, age, race, hospital, and year of interview (160 malignant, 112 nonmalignant) From 18 hospitals in six U.S. cities	Lifetime occupational history Self-reported diesel exhaust exposure Exposure aggregated a priori into: Low probability Possible Probable	No excess found	Exposure based on self-report, which was not validated Although lifetime occupational history was obtained, analysis was restricted to usual occupation A priori classification was ambiguous

Table 8-3. Epidemiologic studies of the health effects of exposure to diesel exhaust: case-control studies of bladder cancer (continued)

Authors	Population studied	Diesel exhaust exposure assessment	Results	Limitations
Steineck et al. (1990)	Population-based study from County of Stockholm Men born between 1911 and 1945 256 (243 bladder) urinary tract cancer incident cases (80% of eligibles) 287 controls (79% of eligibles) from population of Stockholm Observation period September 15, 1985, to November 30, 1987	Occupational history classified into exposed and nonexposed by industrial hygienist "blind" toward case or control status Using all exposure information, annual dose rated as "low," "moderate," and "high"	SNS OR = 1.3 for low, OR = 2.2 for moderate, and OR = 2.9 for high exposure were observed for diesel exposure SNS OR = 7.1 observed for diesel and gasoline exhaust combined exposure	Elaborate exposure history classification not used to advantage by simultaneous adjustment Misclassification in exposure may have occurred Small sample size of only 25 cases and 19 controls were exposed to diesel exhaust Confounding by other exposures not accounted for, except benzene

Abbreviations: OR = odds ratio; RR = relative risks; SNS = statistically nonsignificant; SS = statistically significant.

Because diesel emissions become diluted in the ambient air, it is difficult to study the health effects in the general population. Nonoccupational exposure to diesel exhaust is worldwide in urban areas. Thus, "unexposed" reference populations used in occupational cohort studies are likely to contain a substantial number of individuals who are nonoccupationally exposed to diesel exhaust. Furthermore, the "exposed" group in these studies is based on job titles, which in most instances are not verified or correlated with environmental hygiene measurement. The issue of health effect measurement gets further complicated by the fact that occupational cohorts tend to be healthy and have below-average mortality, usually referred to as the "healthy worker effect." Hence, the usual standard mortality ratios observed in cohort mortality studies are underestimations of real risk.

A major difficulty with the occupational studies considered here was the measurement of the actual diesel exhaust exposure. Because all the cohort mortality studies were retrospective, the assessment of health effects from exposure to diesel exhaust was naturally indirect. In these occupational settings, no systematic quantitative records of ambient air were available. Most studies compared men in job categories with presumably some exposure to diesel exhaust with either standard populations (presumably no exposure to diesel exhaust) or with men in other job categories from industries with little or no potential for diesel exhaust exposure. A few studies have included measurements of diesel fumes, but there is no standard method for the measurement. No attempt is made to correlate these exposures with the cancers observed in any of these studies, nor is it clear exactly which extract should have been measured to assess the occupational exposure to diesel exhaust. All studies have relied on the job categories or self-report of exposure to diesel exhaust. In the studies by Garshick et al. (1987, 1988), the diesel exhaust-exposed job categories were verified on the basis of an industrial hygiene survey done by Woskie et al. (1988a,b). It was found by the investigators that in most cases the job titles were good surrogates for diesel exhaust exposure. Also, in the railroad industry where only persons who had at least 10 years of work experience were included in the study, the workers tended not to change job categories over the years. Thus, a job known only at one point in time was a reasonable marker of past diesel exhaust exposure. Unfortunately, the exposure was only qualitatively verified. The quantitative use of this information would have been much more meaningful. The occupations involving potential exposure to diesel exhaust are miners, truck drivers, transportation workers, railroad workers, and heavy equipment operators.

With the exception of the study by Waxweiler et al. (1973), there have been no known studies of miners to assess whether diesel exhaust is associated with lung cancer. Currently, there are about 385 underground metal mines in the United States. Of these, 250 have been permanently operating, whereas 135 have been intermittently operating (Steenland, 1986). Approximately 20,000 miners are employed, but not all of them are currently working in the

mines. Diesel engines were introduced in the metal mines in the early to mid-1960s. Although all these mines use diesel equipment, it is difficult to estimate how many of these miners were actually exposed to diesel fumes.

Diesel engines were introduced in coal mines at an even later date, and their use is still quite limited. In 1983, approximately 1,000 diesel units were in place in underground coal mines, up from about 200 units in 1977 (Daniel, 1984). The number of units per mine varies greatly; one mine may account for more than 100 units.

Even if it were possible to estimate how many miners (metal and coal) were exposed to diesel exhaust, it would be very difficult to separate out the confounding effects of other potential pulmonary carcinogens, such as radon decay products, heavy metals (such as arsenic, chromium), etc. Furthermore, the relatively short latency period limits the usefulness of these cohorts of miners.

8.5.1. The Cohort Mortality Studies

The cohort studies mainly demonstrated an increase in lung cancer. Studies of bus company workers by Waller (1981), Rushton et al. (1983), and Edling et al. (1987) failed to demonstrate any statistically significant excess risk of lung cancer, but these studies have certain methodological problems, such as small sample sizes, short follow-up periods (just 6 years in the Rushton et al. study), lack of information on confounding variables, and lack of analysis by duration of exposure, duration of employment, or latency that preclude their use in determining the carcinogenicity of diesel exhaust. Although the Waller (1981) study had a 25-year follow-up period, the cohort was restricted to employees (ages 45 to 64) currently in service. Employees who left the job earlier, as well as those who were still employed after age 64 and who may have died from cancer, were excluded.

Wong et al. (1985) conducted a mortality study of heavy equipment operators that demonstrated a significant increased risk of liver cancer in total and in various subcohorts. The same analysis also showed statistically significant deficits in cancers of the large intestine and rectum. Metastases from the cancers of the large intestine and rectum in the liver probably were misclassified as primary liver cancer, which led to an observed excess risk. This study did demonstrate a nonsignificant positive trend for cancer of the lung with length of membership and latency. Analysis of deceased retirees showed a significant excess of lung cancer. Individuals without work histories who started work prior to 1967, when records were not kept, may have been in the same jobs for the longest period of time. Workers without job histories included those who had the same job before and after 1967 and thus may have worked about 12 to 14 years longer; these workers exhibited significant excess risks of lung cancer and stomach cancer. If this assumption about duration of jobs is correct, then these site-specific causes can be linked to diesel

exhaust exposure. One of the methodological limitations of this study is that most of these men worked outdoors; thus, this cohort might have had relatively low exposure to diesel exhaust. The authors did not present any environmental measurement data either. Because of the absence of detailed work histories for 30% of the cohort and the availability of only partial work histories for the remaining 70%, jobs were classified and ranked according to presumed diesel exposure. Information is lacking regarding duration of employment in the job categories (used for surrogate of exposure) and other confounding factors (alcohol consumption, cigarette smoking, etc.). Thus, this study cannot be used to support a causal association or to refute the same between exposure to diesel exhaust and lung cancer.

A 2-year mortality analysis by Boffetta and Stellman (1988) of the American Cancer Society's prospective study, after controlling for age and smoking, demonstrated an excess risk of lung cancer in certain occupations with potential exposure to diesel exhaust. These excesses were statistically significant among miners (RR = 2.67, 95% CI = 1.63, 4.37) and heavy equipment operators (RR = 2.6, 95% CI = 1.12, 6.06). The elevated risks were nonsignificant in railroad workers (RR = 1.59) and truck drivers (RR = 1.24). A dose response was also observed for truck drivers. With the exception of miners, exposure to diesel exhaust occurred in the three other occupations showing an increase in the risk of lung cancer. Despite methodologic limitations, such as the lack of representiveness of the study population (composed of volunteers only, who were probably healthier than the general population), leading to an underestimation of the risk and the questionable reliability of exposure data based on self-administered questionnaires that were not validated, this study is suggestive of a causal association between exposure to diesel exhaust and excess risk of lung cancer.

Two mortality studies were conducted by Gustavsson et al. (1990) and Hansen (1993) among bus garage workers (Stockholm, Sweden) and truck drivers, respectively. An SMR of 122 was found among bus garage workers based on 17 cases. A nested case-control study was also conducted in this cohort. Detailed exposure matrices based on job tasks were assembled for both diesel exhaust and asbestos exposures. Statistically significant increasing lung cancer relative risks of 1.34, 1.81, and 2.43 were observed for diesel exhaust indices of 10 to 20, 20 to 30, and >30, respectively, using 0 to 10 as a comparison group. Adjustment for asbestos exposure did not change the results. The main strength of this study is the detailed exposure matrices; some of the limitations are lack of smoking histories and low power (small cohort).

Hansen (1993), on the other hand, found statistically significant SMR of 160 due to cancer of bronchus and lung. No dose response was observed, although the excesses were observed in most of the age groups (30 to 39, 45 to 49, 50 to 54, 55 to 59, 60 to 64, and 65 to 74). There are quite a few methodologic limitations to this study. Exposure to diesel exhaust was assumed in truck drivers for diesel-powered trucks, but no validation of exposure was attempted. Smoking

data were lacking, follow-up period was short, and no latency analysis was done. The findings of both these studies are consistent with the findings of other truck driver studies.

Two mortality studies of railroad workers were conducted, by Howe et al. (1983) in Canada and Garshick et al. (1988) in the United States. The Canadian study found relative risks of 1.2 ($p<0.01$) and 1.35 ($p<0.001$) among "possibly" and "probably" exposed groups, respectively. The trend test showed a highly significant dose-response relationship with exposure to diesel exhaust and the risk of lung cancer. The main limitation of the study was the inability to separate overlapping exposures of coal dust and diesel fumes. Information on jobs was available at retirement only. There was also insufficient detail on the classification of jobs by diesel exhaust exposure. The exposures could have been nonconcurrent or concurrent, but because the data are lacking, it is possible that the observed excess could be due to the effect of both coal dust and diesel fumes and not due to just one or the other. However, it should be noted that, so far, coal dust has not been demonstrated to be a pulmonary carcinogen in studies of coal miners, but lack of data on confounders such as asbestos and smoking makes interpretation of this study difficult. When three diesel exhaust exposure categories were examined for smoking-related diseases such as emphysema, laryngeal cancer, esophageal cancer, and buccal cancer, positive trends were observed, raising a possibility that the dose-response demonstrated for diesel exposure may have been due to smoking. The findings of this study are at best suggestive of diesel exhaust being a lung carcinogen.

The most definitive evidence for linking diesel exhaust exposure to lung cancer comes from the Garshick et al. (1988) railroad worker study conducted in the United States. Relative risks of 1.57 (95% CI = 1.19, 2.06) and 1.34 (95% CI = 1.02, 1.76) were found for ages 40 to 44 and 45 to 49, respectively, after the exclusion of workers exposed to asbestos. This study also found that the risk of lung cancer increased with increasing duration of employment. As this was a large cohort study with lengthy follow-up and adequate analysis, including dose response (based on duration of employment as a surrogate) as well as adjustment for other confounding factors such as asbestos, the observed association between increased lung cancer and exposure to diesel exhaust is more meaningful.

8.5.2. Case-Control Studies of Lung Cancer

Among the 10 lung cancer case-control studies reviewed in this chapter, only 2 studies did not find any increased risk of lung cancer. Lerchen et al. (1987) did not find any excess risk of lung cancer, after adjusting for age and smoking, for diesel fume exposure. The major limitation of this study was a lack of adequate exposure data derived from the job titles obtained from occupational histories. Next of kin provided the occupational histories for 50% of the cases that were not validated. The power of the study was small (analysis done on males only, 333 cases).

Similarly, Boffeta et al. (1990) did not find any excess of lung cancer after adjusting for smoking and education. This study had a few methodological limitations. The lung cancer cases and controls were drawn from the ongoing study of tobacco-related diseases. It is interesting to note that the leading risk factor for lung cancer is cigarette smoking. The exposure was not measured. Instead, occupations were used as surrogates for exposure. Furthermore, there were very few individuals in the study who were exposed to diesel exhaust. On the other hand, statistically nonsignificant excess risks were observed for diesel exhaust exposure by Williams et al. (1977) in railroad workers (OR = 1.4) and truck drivers (OR = 1.34), by Hall and Wynder (1984) in workers who were exposed to diesel exhaust versus those who were not (OR = 1.4 and 1.7 with two different criteria), and by Damber and Larsson (1987) in professional drivers (OR = 1.2). These rates were adjusted for age and smoking. Both Williams et al. (1977) and Hall and Wynder (1984) had high nonparticipation rates of 47% and 36%, respectively. Therefore, the positive results found in these studies are underestimated at best. In addition, the self-reported exposures used in the study by Hall and Wynder (1984) were not validated. This study also had low power to detect excess risk of lung cancer for specific occupations.

The study by Benhamou et al. (1988), after adjusting for smoking, found significantly increased risks of lung cancer among French motor vehicle drivers (RR = 1.42) and transport equipment operators (RR = 1.35). The main limitation of the study was the inability to separate the exposures to diesel exhaust from those of gasoline exhaust because both motor vehicle drivers and transport equipment operators probably were exposed to the exhausts of both types of vehicles.

Hayes et al. (1989) combined data from three studies (conducted in three different states) to increase the power to detect an association between lung cancer and occupations with a high potential for exposure to diesel exhaust. They found that truck drivers employed for more than 10 years had a significantly increased risk of lung cancer (OR = 1.5, 95% CI = 1.1, 1.9). This study also found a significant trend of increasing risk of lung cancer with increasing duration of employment among truck drivers. The relative odds were computed by adjusting for birth cohort, smoking, and State of residence. The main limitation of this study is again the mixed exposures to diesel and gasoline exhausts, because information on type of engine was lacking. Also, potential bias may have been introduced because the way in which the cause of death was ascertained for the selection of cases varied in the three studies. Further, the methods used in these studies to classify occupational categories were different, probably leading to incompatibility of occupational categories.

The most convincing evidence comes from the Garshick et al. (1987) case-control study of railroad workers and the Steenland et al. (1990) case-control study of truck drivers in the Teamsters Union. Garshick et al. found that after adjustment for asbestos and smoking, the

relative odds for continuous exposure were 1.39 (95% CI = 1.05, 1.83). Among the younger workers with longer diesel exhaust exposure, the risk of lung cancer increased with the duration of exposure after adjusting for asbestos and smoking. Even after the exclusion of recent diesel exhaust exposure (5 years before death), the relative odds increased to 1.43 (95% CI = 1.06, 1.94). This study appears to be a well-conducted and well-analyzed case-control study with reasonably good power. Potential confounders were controlled adequately, and interactions between diesel exhaust and other lung cancer risk factors were tested.

Steenland et al. (1990), on the other hand, created two separate work history files, one from Teamsters Union pension files and the other from next-of-kin interviews. Using duration of employment as a categorical variable and considering employment after 1959 (when presumed dieselization occurred) for long-haul drivers, the risk of lung cancer increased with increasing years of exposure. Using 1964 as the cutoff, a similar trend was observed for long-haul drivers. For short-haul drivers, the trend was positive with a 1959 cutoff but not when 1964 was used as the cutoff. For truck drivers who primarily drove diesel trucks and worked for 35 years, the relative odds were 1.89. The limitations of this study include possible misclassifications of exposure and smoking, lack of levels of diesel exposure, smaller nonexposed group, and insufficient latency period. Given these limitations, the findings of this study are probably underestimated.

Emmelin et al. (1993) in their Swedish dock workers from 15 ports found increased relative odds of 6.8 (90% CI = 1.3 to 34.9). Intricate exposure matrices were created using three different variables, but no direct exposure measurement was done. Of 50 cases and 154 controls, only 6 individuals were nonsmokers. A strong interaction between smoking and diesel exhaust was observed in this study.

8.5.3. Case-Control Studies of Bladder Cancer

Of the seven bladder cancer case-control studies, four studies found increased risk in occupations with a high potential diesel exhaust exposure. A significantly increased risk of bladder cancer was found in Canadian railroad workers (RR = 9.0, 95% CI = 1.2, 349.5; Howe et al., 1980), truck drivers from New Hampshire and Vermont (OR = 2.9, $p<0.05$; Hoar and Hoover, 1985), and in Argentinean truck and railroad drivers (RR = 4.31, $p<0.002$; Iscovich et al., 1987). A positive trend with increasing employment as truck driver ($p=0.006$) was observed by Hoar and Hoover (1985) in their study of truck drivers from New Hampshire and Vermont. Significantly increased risks also were observed with increasing duration of employment of $\geq$20 years in truck drivers (OR = 12, $p=0.01$) and railroad workers (OR = 2.21, $p<0.05$; Steenland et al., 1987). No significant increased risk was found for any diesel-related occupations in studies by Wynder et al. (1985), Iyer et al. (1990), or Steineck et al. (1990). All these studies had several

limitations, including inadequate characterization of diesel exhaust exposure, lack of validation of surrogate measures of exposure, and presence of other confounding factors (cigarette smoking, urinary retention, concentrated smoke within the truck cab, etc.); most of them had small sample sizes and none presented any latency analysis.

8.5.4. Relevant Methodologic Issues

Throughout this chapter various methodologic limitations of individual studies have been discussed, such as small sample size, short follow-up period, lack of latency analysis, and lack of data on confounding variables. However, two of the major methodologic concerns in these studies are use of death certificates to determine the cause of death and lack of data on cigarette smoking, which is a strong risk factor for both lung cancer and bladder cancer. Death certificates were used by all of the seven cohort mortality studies, two case-control studies of lung cancer, and one case-control study of bladder cancer to determine cause of death. Use of death certificates could lead to misclassification bias. Studies of autopsies done between 1960 and 1971 demonstrated that lung cancer was overdiagnosed when compared with hospital discharge, with no incidental cases found at autopsy (Rosenblatt et al., 1971). Schottenfeld et al. (1982) also found an overdiagnosis of lung cancer among autopsies conducted in 1977 and 1978. On the other hand, Percy et al. (1981) noted 95% concordance when comparing 10,000 lung cancer deaths observed in the Third National Cancer Survey from 1969 to 1971 (more than 90% were confirmed histologically) to death certificate-coded cause of death. For bladder cancer, the concordance rate was 91%. These more recent findings suggest that the diagnosis of lung cancer as well as bladder cancer on death certificates is better than anticipated. Furthermore, an overdiagnosis of lung cancer or bladder cancer on death certificates would reduce the ability of the study to detect an effect of diesel exhaust exposure.

All the cohort studies considered for this report are retrospective mortality studies. It is usually difficult to obtain smoking history in such instances. The smoking histories obtained from surrogates (next of kin being either a spouse or an offspring) were found to be accurate by Lerchen and Samet (1986) and McLaughlin et al. (1987). Lerchen and Samet (1986) did not detect any consistent bias in the report of cigarette consumption. In contrast, overreporting of cigarette smoking by surrogates was observed by Rogot and Reid (1975), Kolonel et al. (1977), and Humble et al. (1984). Kolonel et al. (1977) found that the age at which an individual started smoking was reported within 4 years of actual age 84% of the time. The indication from these studies is that surrogates were able to provide fairly credible information on the smoking habits of the study subjects. If the surrogates of the cases were more likely to overreport cigarette smoking as compared to the controls, then it might be harder to find an effect of diesel exhaust because

most of the increase in lung cancer would be attributed to smoking rather than to the effect of exposure to diesel exhaust.

8.5.5. Criteria of Causal Inference

In most situations epidemiologic data are used to delineate the causality of certain health effects. Several cancers have been causally associated with exposure to agents for which there is no direct biological evidence. Insufficient knowledge about the biological basis for diseases in humans makes it difficult to identify exposure to an agent as causal, particularly for malignant diseases when the exposure was in the distant past. Consequently, epidemiologists and biologists have provided a set of criteria that define a causal relationship between exposure and the health outcome. A causal interpretation is enhanced for studies that meet these criteria. None of these criteria actually proves causality; actual proof is rarely attainable when dealing with environmental carcinogens. None of these criteria should be considered either necessary (except temporality of exposure) or sufficient in itself. The absence of any one or even several of these criteria does not prevent a causal interpretation. However, if more criteria apply, it provides more credible evidence for causality.

Thus, applying the criteria of causal inference to the seven cohort mortality and eight case-control studies in which risk of lung cancer was assessed resulted in the following:

- **Temporality:** There is a temporality of exposure to diesel exhaust prior to the occurrence of lung cancer.

- **Strength of association:** The strength of association between exposure and the occurrence of lung cancer in the cohort studies showed a 30% to 57% higher risk among exposed persons as compared to nonexposed (Howe et al., 1983; Wong et al., 1985; Boffetta and Stellman, 1988; Garshick et al., 1988). In case-control studies, the risk varied from 20% to 89% higher among exposed as compared to nonexposed (Williams et al., 1977; Hall and Wynder, 1984; Damber and Larsson, 1987; Garshick et al., 1987; Benhamou et al., 1988; Hayes et al., 1989; Steenland et al., 1990; Gustavsson et al., 1990; Emmelin et al., 1993). Some of these studies did adjust for the confounding effects of smoking, asbestos, and other exposures. Furthermore, a recent publication by HEI (1995) demonstrates this strength of association in graphic presentation (Figures 8-1 and 8-2). Although the studies had smaller increases in lung cancer risk and only some of the studies considered by HEI (1995) are considered in this chapter, it demonstrates the lung cancer excesses consistently all across the various populations.

- **Consistency:** Five cohort studies and nine (including one nested case-control) case-control studies of lung cancer conducted in several populations in the United States and Europe consistently found the same effect (i.e., lung cancer).

- **Specificity:** All of the above-mentioned studies found the same specific effect (i.e., lung cancer).

- **Biological gradient:** The biological gradient, which refers to the dose-response relationship, was observed in the cohorts of Canadian railway workers (Howe et al., 1983), heavy bulldozer operators (Wong et al., 1985), and truck drivers who had enrolled in the American Cancer Society's prospective mortality study (Boffetta and Stellman, 1988). In the case-control studies, a dose response was observed in railroad workers (Garshick et al., 1988; Hayes et al., 1989; Steenland et al., 1990). Although other studies failed to observe a dose response, these studies were methodologically limited due to confounding by other exposures and lack of either quantitative data on exposure or surrogate data on dose.

- **Biological plausibility:** Because diesel exhaust consists of a carbon core particle with surface layers of organics and gases, the tumorigenic activity may reside in one, some, or all of these components. As explained in Chapter 9, there is clear evidence that the organic constituents have the capacity to interact with DNA and give rise to mutations, chromosomal aberrations, and cell transformations, all well-established steps in the process of carcinogenesis. Furthermore, these organic chemicals include a variety of polycyclic aromatic hydrocarbons and nitroaromatics, many of which are known to be pulmonary carcinogens. Alternatively, Vostal (1986) suggests that "diesel" particles themselves induce lung cancer, most likely via an epigenetic mechanism, if they are present at sufficiently high doses. This makes a convincing argument for biological plausibility of lung cancer occurrence under some condition of exposure.

When the same causal inference criteria were applied to the seven case-control studies in which risk of bladder cancer was assessed, the results were:

- **Temporality:** There is temporality of exposure to diesel exhaust prior to the occurrence of bladder cancer.

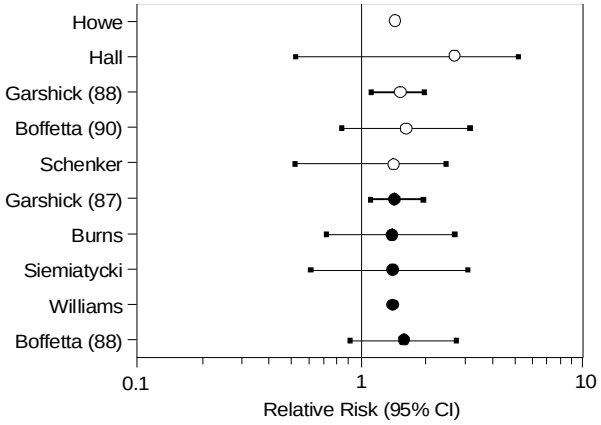

Figure 8-1. Lung cancer and exposure to diesel exhaust in railroad workers. ● = Relative risk adjusted for cigarette smoking; ○ = relative risk not adjusted for cigarette smoking. For the two studies by Howe and Williams, confidence intervals were not reported and could not be calculated.

Source: HEI, 1995.

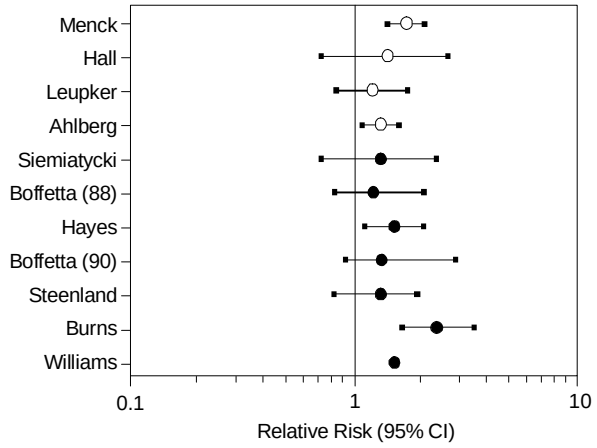

Figure 8-2. Lung cancer and exposure to diesel exhaust in truck drivers. ● = Relative risk adjusted for cigarette smoking; ○ = relative risk not adjusted for cigarette smoking. For the study by Williams, confidence intervals were not reported and could not be calulated. For the Steenland study, the data were gathered from union reports of long-haul truck drivers; for the Boffetta (1988) study, the data were self-reported by diesel truck drivers; and for the Siemiatycki study, they were self-reported by heavy-duty truck drivers (personal communication).

Source: HEI, 1995.

- **Strength of association:** The relative odds of getting bladder cancer among exposed as compared to nonexposed ranged from 2 to 12 times higher (Howe et al., 1980; Hoar and Hoover, 1985; Iscovich et al., 1987; Steenland et al., 1987). None of these studies adjusted for other confounding effects such as cigarette smoking, exposures to other chemicals, urinary retention, etc.

- **Consistency:** Four out of seven bladder case-control studies conducted in the United States and abroad found an increased relative odds of bladder cancer in the exposed population. None of the cohort studies showed increased bladder cancer mortality; however, people rarely die from bladder cancer, so bladder cancer excess is unlikely to be detected in mortality studies.

- **Specificity:** Four out of seven case-control studies found an excess of bladder cancer. The specificity criterion, per se, does not apply in this particular instance because these are case-control studies.

- **Biological gradient:** Dose response was observed in two out of four studies showing increasing relative odds with increasing length of employment (Hoar and Hoover, 1985; Steenland et al., 1987).

- **Biological plausibility:** It has been demonstrated that motor exhaust emissions contain PAHs and nitro-PAHs (Stenberg et al., 1983; Rosenkranz and Mermelstein, 1983). There is some evidence that nitro-PAHs may be responsible for the induction of human bladder cancer. Nitro-PAHs can be metabolized to aromatic amine derivatives, and some of these agents are known to be capable of inducing urinary bladder cancer (Clayson and Garner, 1976). Furthermore, 1-nitropyrene (1-NP) has been reported to be carcinogenic in the rat mammary gland (Hirose et al., 1984); the structurally related 4-aminobiphenyl, which induces bladder cancer in humans, also induces mammary gland tumors in rats (Hirose et al., 1984). Although the applicability of these experimental results to humans is unknown, the laboratory evidence certainly suggests the biological plausibility of diesel exhaust to be a urinary bladder carcinogen.

In summary, although some of the causality inference criteria do apply to bladder cancer, the evidence for bladder cancer in populations exposed to diesel exhaust is inadequate. On the other hand, all the causality inference criteria apply well to lung cancer. An excess risk of lung cancer was observed in four out of seven cohort studies and seven out of eight case-control studies. Dose response was found in three cohort studies and three case-control studies using duration of employment as a surrogate for dose. A recent meta-analysis (Bhatia, 1998) shows the consistency of elevated risks in 23 of 29 diesel exposure epidemiology studies, with statistically significant relative risks of 1.33. However, because of lack of actual data on exposure to diesel exhaust in these studies and other subtle methodologic limitations, the human evidence falls just short of being sufficient to call diesel exhaust a human carcinogen. Using EPA's 1986 *Guidelines*

for Carcinogen Risk Assessment, the human evidence alone is "limited," however, the "limited" classification doesn't indicate how close this is to being a known human carcinogen. Although diesel exhaust exposure is classified as "Limited," the human evidence is highly suggestive of a causal association between lung cancer and occupational exposure. Based on the human evidence alone, diesel exhaust is close to being a known human carcinogen.

8.6. REFERENCES

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